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THE PROJECTION OF MUSCLE AFFERENTS FROM THE HAND TO CEREBRAL CORTEX IN MAN

by S. C. GANDEVIA, DAVID BURKE *and* BRIAN McKEON

(*From the Unit of Clinical Neurophysiology, Department of Neurology, The Prince Henry Hospital and School of Medicine, University of New South Wales, Sydney, Australia 2033*)

SUMMARY

This study provides direct evidence that muscle afferents from the human hand project to the cerebral cortex. Electrical stimulation within a purely muscle fascicle of the median nerve at the wrist produced a cerebral potential, the latency of which (to the initial negative deflection, N1) was the same as, or shorter than, the latency with stimulation of cutaneous fascicles. The average latencies to N1 for muscle afferent and cutaneous afferent inputs were 19.0 and 20.3 ms, respectively. This difference could not be accounted for by differences in peripheral conduction velocity. The site of the maximal initial negative deflection of the cerebral potential for muscle afferents was posterior to that for cutaneous afferents. This locus for muscle afferents corresponded to that for mixed afferent inputs. Muscle afferents contribute to, and may dominate, the cerebral potential produced by stimulation of the mixed median nerve at the wrist.

INTRODUCTION

After early suggestions that group I afferents from muscle do not project to the cerebral cortex (Mountcastle *et al.*, 1952; McIntyre, 1953; *see also* Rose and Mountcastle, 1959), evidence that they have a cortical projection subsequently came from electrophysiological studies in cats (Oscarsson and Rosén, 1963; Landgren and Silfvenius, 1969). A projection of low threshold muscle afferents to cortical levels was then demonstrated in nonhuman primates (*see* Albe-Fessard *et al.*, 1965; Phillips *et al.*, 1971; Lucier *et al.*, 1975; Hore *et al.*, 1976). In man, there is an accumulation of psychophysical data indicating that low threshold intramuscular receptors contribute to proprioceptive sensations (Goodwin *et al.*, 1972; Gandevia and McCloskey, 1976; for review, *see* McCloskey, 1978; Matthews, 1982). Muscle afferents may also be involved in long-latency, possibly transcortical reflexes (Phillips, 1969; Marsden *et al.*, 1973; Lee and Tatton, 1975; Chofflon *et al.*, 1982). It is therefore important to confirm that muscle afferents do project to cerebral cortex in man and, if so, to determine the latency of that projection.

There have been many reports of the cerebral potential produced by stimulation of the median nerve at the wrist (Dawson, 1947*a*; Allison, 1962; Giblin, 1964); some have concentrated on the cerebral potential of cutaneous origin using digital nerve stimulation (*see* Debecker and Desmedt, 1964; Rushton *et al.*, 1981), others on mechanical stimulation of digital skin (Pratt *et al.*, 1979; Gandevia *et al.*, 1983). However, there are few studies which have looked specifically for a cerebral potential from muscle afferents in the human median nerve. In his pioneering work on evoked cerebral potentials, Dawson (1947*b*) described a patient with myoclonus in whom the myoclonic jerks produced by tendon percussion were associated with large cerebral potentials over the contralateral cortex. Similar findings have been reported for another patient in whom the precipitating stimulus probably involved muscle afferents in the biceps, brachioradialis and forearm muscles on one side (Rosén *et al.*, 1977). In other patients with 'cortical reflex myoclonus' (Hallett *et al.*, 1979), cutaneous stimuli alone (Sutton, 1975) or mixed cutaneous and muscle stimuli (Kugelberg and Widén, 1954; Sutton and Mayer, 1974) were associated with the myoclonic jerks and large cerebral potentials. These studies revealed in a striking way the potential strength of the short latency projection from peripheral afferents to cortex although, for any one patient, it is difficult to determine with certainty the class(es) of receptors responsible.

Mechanical activation of receptors in muscles of the lower limb or electrical stimulation of their afferents can produce a stable cerebral potential in normal human subjects (Starr *et al.*, 1981; Burke *et al.*, 1981, 1982). Indeed, the cerebral potential evoked by electrical stimulation of the posterior tibial nerve is largely, if not exclusively, determined by the activity in muscle afferents. Cutaneous afferent activity appears to contribute little to the cerebral potential, due to inhibition set up by the more rapidly conducting muscle afferents at relay nuclei in the somatosensory pathway (Burke *et al.*, 1982). However, it cannot be assumed that the situation is similar with upper limb nerves, such as the median nerve at the wrist, for the following reasons. First, there is no detectable difference in conduction velocities of the fastest cutaneous afferents and the fastest afferents in the mixed nerve (Buchthal and Rosenfalck, 1966). Secondly, the median nerve at the wrist contains more fascicles innervating skin than muscle (Sunderland and Bedbrook, 1949; Sunderland, 1968). Thirdly, muscle afferents from thenar muscles have a longer central pathway because they traverse the C8/T1 posterior roots whereas the cutaneous afferents from the index and thumb enter the spinal cord at a higher level.

In this study cerebral potentials have been recorded to stimulation of individual fascicles of the median nerve at the wrist. The cerebral potentials evoked by stimulation of muscle afferents in isolation and of cutaneous afferents in isolation have been compared to that evoked by stimulation of the whole nerve. It has been found that volleys in muscle afferents from the thenar muscles do project along a short-latency path to the cerebral cortex, and that the cerebral potential they produce constitutes a major component of the potential produced by stimulation of the whole nerve.

METHODS

Experiments were performed on four subjects, including two of the authors. All gave informed consent to the experimental procedures. Subjects lay supine on a bed or reclined comfortably in a padded chair with head supported. Peripheral and cerebral potentials produced by stimulation of isolated cutaneous and muscle fascicles were compared with those produced by stimulation of the whole median nerve at the wrist in the same experiment.

Stimulus and Recording Techniques

Fine tungsten microelectrodes were inserted into the median nerve 2 to 3 cm proximal to the wrist and guided into fascicles which innervated either skin or muscle, exclusively. The techniques have been described in detail elsewhere (*see* Vallbo *et al.*, 1979). Muscle fascicles were characterized by (1) twitch contractions of the innervated muscles in response to weak stimuli delivered through the microelectrode; (2) the absence of cutaneous paraesthesiae with strong intrafascicular stimulation; (3) profuse neural activity in response to taps on the muscle belly, to movements which stretched the muscle and to weak isometric voluntary contractions; (4) the absence of neural responses to cutaneous stimuli; and (5) the presence of sympathetic efferent activity in discrete bursts synchronous with the pulse (Vallbo *et al.*, 1979). Cutaneous fascicles were characterized by (1) cutaneous paraesthesiae locked to the intrafascicular stimuli; (2) the absence of a muscle twitch in response to stimulation through the microelectrode; (3) the presence of multiunit activity in response to mild tactile stimuli; and (4) sympathetic efferent activity which came in bursts of irregular duration, unrelated to the pulse. To produce cerebral potentials stimuli of 0.2 ms duration were delivered at 2 Hz through the intrafascicular microelectrode at a level which produced either a forceful twitch of the thenar eminence without cutaneous paraesthesiae (muscle fascicles) or nonpainful paraesthesiae restricted to the cutaneous innervation zone of the fascicle (cutaneous fascicles). Stimulus levels ranged from 0.5 to 2.0 V.

The evoked neural volley was recorded over the brachial plexus using a stainless steel subdermal needle electrode at Erb's point, referenced to the forehead. Cerebral activity was recorded using similar electrodes. The active scalp electrode was located routinely 2 to 3 cm posterior to C3 or C4 of the International 10–20 System. A frontal reference was used to minimize the contribution from subcortical and midline generators. In two experiments an array of needle electrodes was used over the scalp. Seven electrode positions were used: 4 were located at 2 cm intervals posterior to C4, and 3 were placed in a similar row at 2 cm intervals with the most anterior electrode 2 cm below and 2 cm posterior to C4.

The evoked activity was amplified (× 100 000), filtered (8 to 800 Hz) and averaged over 50 ms using a fixed-programme averager with an artefact reject facility. The sampling rate was 10 kHz. Usually 1024 or 2048 responses were averaged. In addition, all data were recorded on tape and reanalysed off-line to check that the latencies of the nerve potential recorded over the brachial plexus at Erb's point and of the cerebral potential were stable during the recording period. This was done by comparing the latency and waveform of the potentials in blocks of 256 or 512 sweeps during each run.

Peripheral and cerebral responses to stimulation of the whole median nerve were recorded at least twice during an experiment. A needle electrode was placed subdermally over the median nerve at the wrist, at the level of microelectrode penetration. Stimuli were cathodal pulses (duration 0.2 ms) delivered at a rate of 2 Hz. Care was taken that stimulation of the whole median nerve produced both a twitch of the thenar muscles and radiating cutaneous paraesthesiae in the distribution of the median nerve. Because the study was designed to look at the latency of the peripheral and cerebral responses, stimuli were delivered at strong, but not painful, levels.

Experimental Sequence

The aim was to compare the peripheral and cerebral potentials produced by stimulation of the whole nerve, a cutaneous fascicle and a muscle fascicle in the one experiment under identical conditions. In the first two experiments, potentials to whole nerve stimulation were initially recorded, followed by isolation and study of a cutaneous and then a muscle fascicle, with repetition of stimulation to the whole nerve at the end of each experiment. In the remaining four experiments, because of the time required to isolate a specific fascicle, the response to whole nerve stimulation was recorded after isolation of one or more cutaneous fascicles and again after isolation of a muscle fascicle. Adjustment of the ambient temperature throughout each experiment ensured that skin temperature remained within 0.5° C. All latencies were determined from sequences in which limb temperature was stable. Temperatures, measured on the proximal skin fold over the volar aspect of the wrist, were 29.5 to 32.5° C.

Latencies to mixed nerve stimulation differed by less than 0.2 ms for the cerebral and 0.1 ms for peripheral potentials in the two or more repetitions during an experiment. In the peripheral nerve recordings the latencies to the onset and peak of the negative deflection were measured, and in the cerebral recordings the latencies of the first negative peak (N1) and first positive peak (P1) were measured. These peaks correspond to N19 and P23 using the nomenclature of Donchin *et al.* (1977).

RESULTS

In 6 experiments on 4 subjects, recordings were made from 13 identified fascicles in the median nerve at the wrist. In each experiment recordings were made from one fascicle innervating the thenar muscles and at least one innervating the skin of the thumb, thenar eminence or radial side of index finger. The latencies of the cerebral potentials produced by stimulation within these fascicles were compared with the latency produced by stimulation of the whole nerve with a subdermal electrode positioned immediately adjacent to the intrafascicular microelectrode at the wrist.

Cerebral Potentials Produced by Stimulation of Muscle Afferents

A well-formed cerebral potential was recorded in response to stimulation within each of the 6 fascicles which innervated thenar musculature (figs. 1 and 2). The

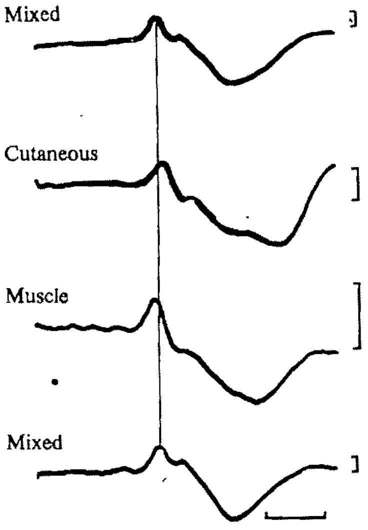

FIG. 1. Cerebral potentials produced by stimulation within a cutaneous fascicle, within a muscle fascicle, and during stimulation of the mixed median nerve at the wrist (*Subject 1*). Traces are shown in the order in which they were obtained in the experiment. A vertical line is drawn at 20.0 ms. Latency to the initial negative deflection (N1) for the cutaneous afferents exceeds that for either muscle or mixed nerve stimulation. In this and subsequent figures a negative deflection is represented as upwards. Cerebral potentials are the average of 1024 and 256 responses to intrafascicular stimulation and mixed nerve stimulation, respectively. The vertical calibration is 2 μV and the time calibration is 10 ms.

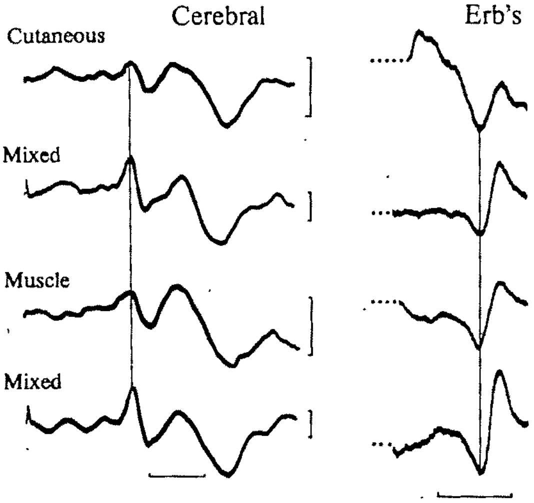

FIG. 2. Cerebral potentials (*left*) and corresponding nerve potentials recorded at Erb's point (*right*) from experiment 2(A) (*see* Table). There was little difference in latency of the cerebral potentials according to whether a muscle fascicle, a cutaneous fascicle or the whole median nerve was stimulated. The latencies of the nerve potentials at Erb's point are also similar. Potentials to intrafascicular stimulation and to mixed nerve stimulation are the averages of 1024 and 256 responses, respectively. For cerebral potentials the horizontal calibration is 10 ms and vertical calibration is 4 μV. For potentials recorded at Erb's point the horizontal calibration is 5 ms and the vertical calibration is 1 μV.

earliest reproducible response consisted of a negative peak (N1) at about 20 ms and a subsequent positive peak at about 23 ms (P1). The later components of the potential were similar in shape and latency to those previously described for stimulation of the whole median nerve (*see below*). The average latency of N1 was 19.0 ms (n = 6; range 17.1 to 20.4 ms; *see* Table).

TABLE. LATENCIES (IN MS) TO N1 AFTER STIMULATION OF THE WHOLE MEDIAN NERVE, MUSCLE FASCICLES AND CUTANEOUS FASCICLES

Subject	*Mixed*	*Muscle*	*Cutaneous*
1	20.0	20.0	21.2
2(A)	19.5	19.6	19.8
			20.1
2(B)	18.0	18.0	*
3(A)	20.4	19.5	21.6
			21.0
3(B)	19.5	18.9	20.7
4	17.1	17.7	17.7
Mean	19.1	19.0	20.3

* In this experiment, the distributions of the cutaneous and muscle potentials were mapped; the cutaneous potential was obtained by stimulation of a digital nerve of the index finger, rather than by intrafascicular stimulation.

Cerebral Potentials Produced by Stimulation of Cutaneous Afferents

Well-formed cerebral potentials were recorded in response to stimulation within each of 7 fascicles which innervated skin. Four fascicles innervated skin along the radial aspect of the index finger, two innervated small areas of skin over the thenar eminence and the remaining fascicle innervated the radial aspect of the thumb. These fascicles were chosen because they are probably innervated by the C6 (±C7) posterior roots, in contrast to innervation of the thenar muscles (C8, T1). There were no obvious differences in the cerebral potentials according to the cutaneous zone innervated by the stimulated fascicle. The average latency to the onset of the first negative peak was 20.3 ms (n = 7; range 17.7 to 21.6 ms; *see* Table).

Comparison of Latency of N1 for Cutaneous, Muscle Afferent and Whole Nerve Stimulation

One purpose of this study was to determine whether the latency of the earliest component of the cerebral potential produced by stimulation of the mixed median nerve reflected activity in cutaneous afferents, muscle afferents or both classes of afferent. In the four subjects the latency of N1 produced by stimulation of muscle afferents in the median nerve was the same as, or less than, that produced by stimulation of cutaneous afferents in the same nerve. In Subjects 1 and 3 the muscle afferents had a shorter conduction time to cortex than cutaneous afferents, the average differences in latency of N1 being 1.2 and 1.8 ms, respectively (*see* fig. 1 and the Table). In Subject 2, muscle afferents were slightly faster than cutaneous afferents (two fascicles, 0.2 and 0.5 ms latency difference for N1). In Subject 4 there was no difference in the latencies of N1 (*see* Table).

The latencies of N1 with whole nerve stimulation were the same as with intrafascicular stimulation of muscle afferents in two subjects (Subjects 1 and 2 in the Table). In one subject (Subject 3) the latency with muscle afferent stimulation was consistently less than that with whole nerve stimulation. In the remaining subject the latencies with stimulation of muscle or cutaneous afferents were the same, although longer than with stimulation of the whole median nerve. Thus in all subjects the afferent input from muscle reaches the cortex rapidly, at least as fast as cutaneous afferent activity, and probably contributes to the cerebral activity following stimulation of the whole median nerve at the wrist.

Scalp Location of the Cerebral Potentials Produced by Cutaneous and Muscle Afferent Stimulation

In Subjects 2 and 4 a map of the earliest component of the cerebral potential to the different inputs was obtained with a grid of seven electrodes extending posteriorly and inferiorly from C4; the electrode separation was 2 cm (*see* Methods). These two subjects were chosen because each had little difference in the latencies of the cerebral potentials to stimulation of purely muscle afferents and purely cutaneous afferents. Amplitudes of the cerebral potentials were expressed as a percentage of the maximal

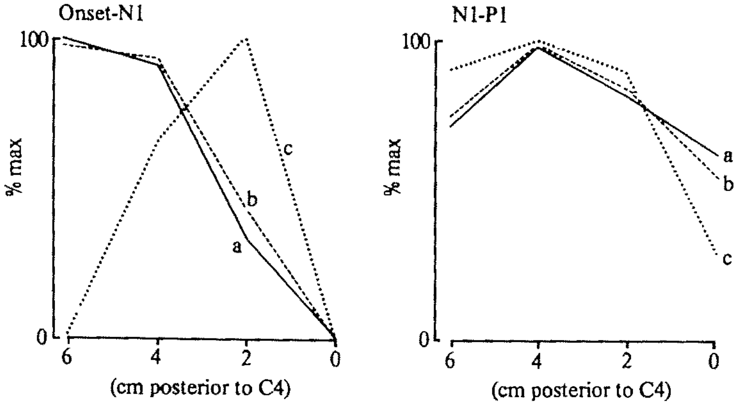

FIG. 3. Relative sizes of the onset-N1 (*left*) and N1-P1 amplitudes (*right*) for *Subject 2* recorded at different locations with a row of electrodes positioned at 2 cm intervals posterior to C4. Solid lines represent the potential produced by stimulation of the whole median nerve (a), dashed lines the muscle potential (b), and the dotted lines the cutaneous potential (c). The maximal size of the onset-N1 amplitude is located more posteriorly for the muscle afferent and the mixed nerve potential than for the cutaneous one.

responses obtained from the array of electrodes (fig. 3). The locus for maximal amplitude of N1 to stimulation of muscle afferents alone and to whole nerve stimulation was posterior to that for maximal N1 to stimulation of cutaneous afferents. The locus at which the N1-P1 deflection was maximal coincided for cutaneous, muscle and mixed stimulation. The maximal locus for N1-P1 was anterior to that for N1 to mixed nerve stimulation. For Subject 2 the maximal amplitude of N1 to stimulation of muscle afferents or the whole median nerve occurred about 4 cm posterior to the site of maximal amplitude of N1 to stimulation of cutaneous afferents (fig. 3). The results for Subject 4 were essentially the same, the difference in the scalp localization of the cutaneous and muscle afferent projections being 2 to 4 cm.

Peripheral Conduction in Cutaneous and Muscle Afferents in the Upper Limb

In the lower limb, muscle afferents have a faster peripheral conduction velocity than cutaneous afferents (or motor efferents; *see*, for example, Burke *et al.*, 1981); this is reflected in the shorter latency of the muscle than cutaneous afferent cerebral potential when nerves in the lower limb are stimulated at comparable distances from the spinal cord (Burke *et al.*, 1981, 1982). Potentials recorded at Erb's point during intrafascicular stimulation did not indicate a similar difference in conduction velocities for the upper limb. The onset of activity at the brachial plexus was the same with the two types of intrafascicular stimulation in Subjects 2 and 4 (fig. 2, *right*). In all four subjects the latency of onset of the mixed potential was the same as that of the muscle afferent potential. However, in Subjects 1 and 3 it was difficult to define a clear onset to the cutaneous potential at Erb's point.

Further comparisons of conduction velocities were made with standard nerve conduction techniques to record conduction time between the elbow and Erb's point for a cutaneous volley produced by stimulation of a digital nerve with ring electrodes on the proximal phalanx of the index finger and for a mixed afferent volley produced by stimulation of the median nerve at the wrist. For each of the four subjects conduction time of the mixed nerve action potential was comparable to that for cutaneous afferents measured over the same segment. This is shown in fig. 4 for Subject 1, in whom the latency of N1 of the cerebral potential produced by stimulation of cutaneous afferents exceeded that of muscle afferents. Fig. 1 illustrates the cerebral potentials from the same subject. With these techniques the most rapidly conducting cutaneous afferents from the index finger had the same conduction velocity as the most rapidly conducting afferents in the mixed nerve.

Interpretation of the results with intrafascicular stimulation and with surface stimulation would be complicated if the most rapidly conducting fibres in the muscle fascicles were efferent fibres. Dawson (1956) has shown (and it was confirmed here) that the motor conduction velocity in the median nerve was less than for the most rapidly conducting fibres in the mixed nerve action potential over the elbow to wrist segment. In the present study conduction velocity of the fastest efferents was about 5 m/s slower (range 4 to 7 m/s) than that of the fastest afferents in the mixed nerve. It is possible that a small degree of contamination of the peak of the mixed nerve action potential occurred as a result of activation of motor efferent axons during stimulation within a muscle fascicle or during stimulation of the whole mixed nerve at the wrist. However, throughout this study conduction velocities were measured to the onset rather than the peak of neural activity.

It is concluded that differences in peripheral conduction velocity do not contribute to the difference in latencies of the cerebral potentials noted in this study. This contrasts with the situation in the lower limb where much of the difference in latency of the cutaneous and muscle afferent cerebral potentials is attributable to

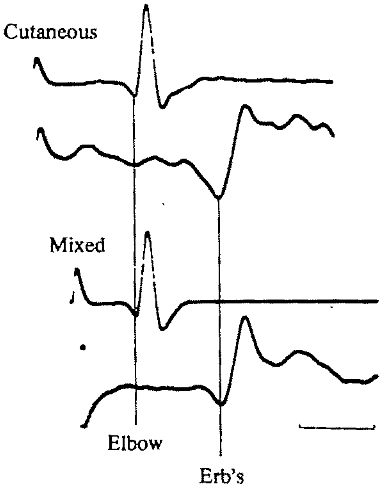

FIG. 4. Peripheral nerve conduction in *Subject 1* on stimulation of the digital nerves of the index finger (*upper two traces*) and on stimulation of the median nerve at the wrist (*lower two traces*). Recordings were made at the elbow (*upper trace in each pair*) and over the brachial plexus at Erb's point (*lower trace in each pair*). Traces are aligned so that the conduction times over the elbow to Erb's point segment can be compared. There was no difference in the conduction times of the fastest cutaneous fibres and the fastest fibres in the mixed nerve action potential. Cerebral potentials for this subject are shown in fig. 1: the muscle afferent potential has a shorter latency than the cutaneous afferent potential. The horizontal calibration is 5 ms. The amplitude of the cutaneous potential is 7 μV at the elbow and 2 μV at Erb's point. The amplitude of the mixed nerve potential is 50 μV at the elbow and 9 μV at Erb's point.

differences in peripheral conduction velocity (Burke *et al.*, 1981). Subject 2 had the greatest difference in latency between the cerebral potentials produced by cutaneous and by muscle afferents in the upper limb but the least difference in latency in the lower limb (Burke *et al.*, 1981). Since peripheral and central factors can contribute to the latency difference in the lower limb but only central factors are important in the upper limb, the discrepancy noted for Subject 2 is not surprising.

DISCUSSION

This study represents the first demonstration of a cerebral projection for muscle afferents from the upper limb in man. Conduction along the muscle afferent pathway is at least as fast as, and in some subjects faster than, along the cutaneous pathway. It is therefore likely that activity in group I muscle afferents dominated the activity evoked in these experiments. Our results also indicate that cutaneous and muscle afferents project to different areas of cerebral cortex, as is known to occur in primates.

The present findings might have been expected from primate studies which have revealed a projection from muscle afferents to the sensorimotor cortex (*see* Phillips *et al.*, 1971; Lucier *et al.*, 1975; Hore *et al.*, 1976) and are compatible with human psychophysical experiments which have shown that afferents from muscle provide sensations of limb position and movement (*see* Goodwin *et al.*, 1972; Gandevia and McCloskey, 1976; Roland and Ladegaard-Pedersen, 1977). The latency of the cerebral potential produced by stimulation of muscle afferents was either the same as, or less than, the latency of the potential produced by stimulation of cutaneous afferents. These results imply that the earliest cerebral activity produced in response to stimulation of the median nerve at the wrist may be determined by activity in muscle afferents. The risk in using the latency (or amplitude) of the early components of the cerebral potential produced by mixed median nerve stimulation as an indicator of the integrity of purely cutaneous paths is obvious.

If, as this study suggests, transmission of muscle afferent signals to cerebral level may occur more rapidly than transmission of cutaneous afferent signals, the reason is not clear. The potentials recorded at the brachial plexus to intrafascicular stimulation and the conventional nerve conduction studies did not reveal any difference in peripheral conduction velocities of cutaneous and muscle afferents in the human upper limb. This confirms a previous study by Buchthal and Rosenfalck (1966). Interestingly, similar findings have been reported for monkeys by Maendly *et al.* (1981). In this study the latency to the thalamic relay for group I muscle afferents in the deep radial nerve was 1.4 ms less than for cutaneous afferents in the superficial radial nerve, a finding which could not be explained fully by differences in peripheral conduction velocity. It is therefore possible that muscle afferent information traverses an effectively shorter path to the cortex or that the number of intervening synapses is less along its path. This is contrary to what might be expected if the segmental entry into the spinal cord for cutaneous and muscle afferents is considered. Thenar muscle afferents presumably enter *via* the C8 and T1 posterior roots while cutaneous afferents of the median nerve enter *via* C6 and C7. Muscle afferents would therefore be expected to have a longer central pathway to cortex.

Comparable human studies on cutaneous and muscle afferents in the lower limb suggest that the early components of the cerebral potential produced by stimulation of the mixed posterior tibial nerve result from activity in muscle afferents (Burke *et al.*, 1981, 1982). In this instance, cutaneous afferents may fail to contribute to the early components because their slower conduction velocity allows the faster muscle afferents to exert active inhibition at subcortical relay nuclei. In the present experiments evidence for a comparable interaction between cutaneous and muscle afferents was not sought, but the size of the cerebral potentials during stimulation of single cutaneous fascicles, single muscle fascicles, and the whole median nerve suggest that a 'suppressive' interaction may have been occurring. The amplitude of the cerebral potentials to stimulation of all afferents in the median nerve at the wrist was the same as would be expected by summation of the potentials produced by about four individual fascicles (*see* calibrations in figs. 1 and 2). That the cerebral potential produced by stimulation of the whole median nerve is not as large as might be expected on the basis of an additive contribution from each of its fascicles probably results from occlusion due to convergence at relay nuclei of the somatosensory pathway. Recent evidence suggests that there is a functionally significant convergence between cutaneous afferents from the index and middle fingers in man with suppression, summation or facilitation depending on the level of stimulation (Gandevia *et al.*, 1983). In the present study the relatively strong levels of stimulation used to aid definition of the cerebral and peripheral potentials would favour occlusion.

One notable finding in the present study was the apparently different cortical projection sites for muscle and cutaneous afferents. The initial negative deflection (N1) was maximal for muscle afferents 2 to 4 cm posterior to the site at which the initial negative deflection for stimulation of cutaneous afferents was maximal. The latter finding for cutaneous afferents in the median nerve is in agreement with a recent study by Rushton *et al.* (1981) in which the locus of the 'primary complex' of the cerebral potential to stimulation of the digital nerves of the thumb was slightly anterior to C4 (International 10–20 System). This does not imply that the cortical generators were necessarily separated by 2 to 4 cm but would be explained by a difference in the geometry of the dipole generators for the cutaneous and muscle afferent projections. This could arise from different strengths of projection and/or sites of projection for the cutaneous and muscle afferents in the pericentral cortex. The initial negative component of the cerebral potential to mixed nerve stimulation (and to purely muscle afferent stimulation) was maximal posterior to the site for cutaneous afferents. Hence, in the present study the onset of cerebral activity after stimulation of the whole median nerve may have been dominated or determined by activity in muscle afferents in all subjects—not only in the two subjects for whom there was a clear difference in latency between the cutaneous and muscle afferent projections, but also in the two for whom the cerebral focus for mixed and muscle afferent inputs differed from that for cutaneous inputs.

ADDENDUM

A recent study by Mauguière *et al.* (*Brain*, 1983, **106**, 271-311) has highlighted the use of an earlobe reference electrode to dissociate the early pre- and post-rolandic components of cerebral potentials produced by stimulation of digital nerves or of the median nerve at the wrist. Use of a frontal reference, as in our experiments, could therefore produce distortion of a projection map. However, this would not invalidate the results of the present study, namely, that muscle afferents from the hand do project to cortex, that they may do so more rapidly than cutaneous afferents, and that their cortical projection is not identical to that of cutaneous afferents.

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DELAYED DETERIORATION FOLLOWING MILD HEAD INJURY IN CHILDREN

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SUMMARY

A series of 42 children is described who, following a seemingly minor or trivial head injury, developed neurological signs after a lucid or symptom-free period. This group constitutes 4.34 per cent of 967 consecutive patients aged 2 months to 17 years who were seen by members of the neurological staff during the years 1978–1981.

Only one patient had an intracranial haematoma. The majority of patients showed a benign transient syndrome consisting of either convulsive or nonconvulsive signs with a spontaneous and full recovery. There were, however, 3 deaths in this series, apparently due to severe and uncontrollable unilateral or diffuse brain swelling, demonstrating the malignant counterpart of this benign syndrome.

The theories seeking to explain these phenomena are reviewed. Special reference is made to the hypotheses of Bruce and his associates regarding brain swelling as a causative factor. It is considered that an adequate theory to explain the pathogenesis is still lacking.

It is concluded that the juvenile brain responds to cranial trauma in a manner different from the adult brain. This implies a different approach in policy to hospital admission.

INTRODUCTION

It is a well established fact that children with head injuries who deteriorate following a lucid interval usually do not have an expanding intracranial haematoma, unlike adults where secondary deterioration following trauma is a strong indication that such a haematoma is present (Walton and Brooks, 1897; Pickles, 1949; Lindenberg *et al.*, 1955; Galbraith and Smith, 1976; James, 1979; Bruce *et al.*, 1979, 1981*a*).

Secondary deterioration not due to intracranial haematoma has been attributed to acute cerebral oedema (Pickles, 1949; Biemond, 1970), convulsions (Small and Woolf, 1957; Livingston and Mahloudji, 1961; Grand, 1974; Reilly *et al.*, 1975; Rose *et al.*, 1977), spreading depression of Leão (Oka *et al.*, 1977), a migrainous mechanism (Haas *et al.*, 1975), a functional disturbance of the rostral brainstem (Todorow and Feller, 1982), concomitant viral meningoencephalitis (Peters *et al.*, 1978), complicating meningitis (Rose *et al.*, 1977) or to unknown causes (Plum and Posner, 1980), whereas recent reports deal with the syndrome of diffuse cerebral swelling, which is attributed to acute cerebral hyperaemia (Langfitt and Bruce, 1975; Bruce *et al.*, 1979, 1981*a*, *b*). The CT scans of children with this diffuse cerebral swelling show a diminution or obliteration of the cerebral ventricles and the perimesencephalic cisterns, whereas the hyperaemia is related to increased CT attenuation numbers of the deep frontal white matter (Zimmerman *et al.*, 1978).

The present study was undertaken in order to investigate retrospectively the incidence of lucid or symptom-free periods in a consecutive series of head-injured children, to describe the different clinical pictures presented by these patients and to correlate the clinical findings with the results of both EEG and CT studies.

PATIENTS AND METHODS

The University Hospital of Groningen has approximately 1100 beds and serves a population of 400000 for primary referrals and 2 million for secondary referrals.

In 1972 a Head Injury Research Study was set up in collaboration with neurosurgical centres in Rotterdam, Glasgow and Los Angeles (Jennett *et al.*, 1977). All injured patients in whom a head injury is suspected are seen by staff of the Neurology Department at the Accident and Emergency Clinic and assessed in a uniform way, using the Glasgow Coma Scale (Teasdale and Jennett, 1974). In order to study the occurrence of lucid or symptom-free periods in children after head injury, the records of all head-injured children (aged 0 to 17 yrs), seen during the years 1978–1981, were reviewed. During this period a total of 967 patients in this age group were seen as primary referrals, that is, not having previously been admitted to another hospital. The neurological assessment usually took place within 1 or 2 h after the accident, in all cases within 24 h.

Patients were included in the present series if, after a head injury not causing unconsciousness or only a very brief period of unconsciousness (not exceeding 5 min), this symptom-free period was followed by a subsequent deterioration of the level of consciousness or by the onset of focal neurological signs, or both. The clinical findings of these patients were compared with the EEGs, skull radiographs and CT scans if available. Where appropriate, attenuation numbers expressed as EMI units of the deep frontal white matter were obtained as described by Zimmerman *et al.* (1978). These attenuation values were compared with those of an appropriate control group of children. Average CT attenuation numbers of the deep frontal white matter in a series of control scans, as will be described later in this paper, ranged from 11.7 EMI units (SD 2.08) to 19.5 EMI units (SD 2.42).

RESULTS

Fig. 1 shows the characteristics of the group of 967 consecutive juvenile patients. Of these, 5 were either dead on arrival or died within a few minutes afterwards. Fig. 2 shows the age distribution of the remaining 962 patients. These patients have been classified according to the Abbreviated Injury Scale (AIS; Ommaya, 1979), which is summarized in Table 1. Because post-traumatic amnesia is usually difficult to assess in children (especially in the younger ones), only the estimated period of unconsciousness has been taken into account.

As fig. 1 shows, 5 patients with linear skull fractures were not admitted, usually because the head injury had occurred more than 12 h previously. Of all admitted patients, 22 died (5.7 per cent), death being attributable to primarily extracranial lesions in 4 cases.

In a total of 40 children a history of a lucid or symptom-free period was found following a head injury which had caused no immediate loss of consciousness. This group of patients meets the criteria of a 'trivial injury' according to Jennett (1962, 1975) (no amnesia, haematoma or skull fracture, or linear fracture only). Two cases

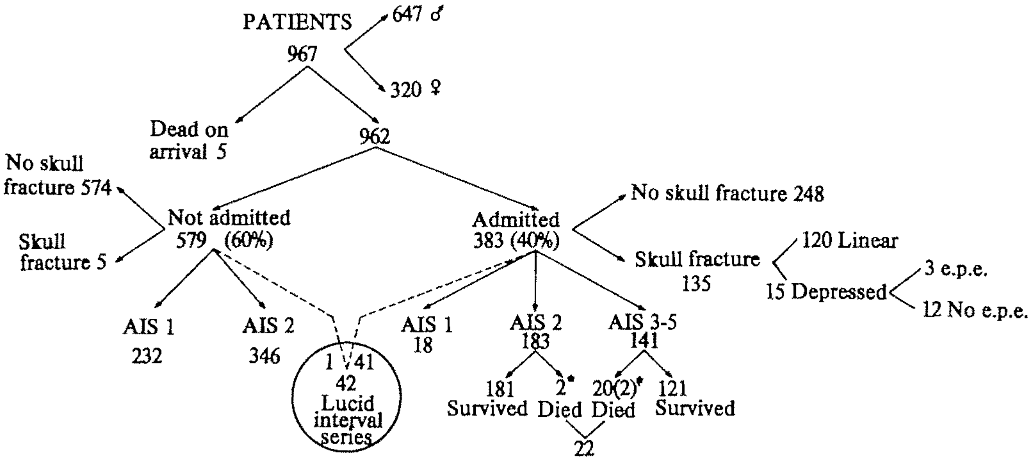

FIG. 1. Characteristics of the group of 967 consecutive patients, aged 2 months to 17 years. AIS = Abbreviated Injury Scale (*see text*). e.p.e. = early post-traumatic epilepsy. * = death attributable primarily to extracranial injuries.

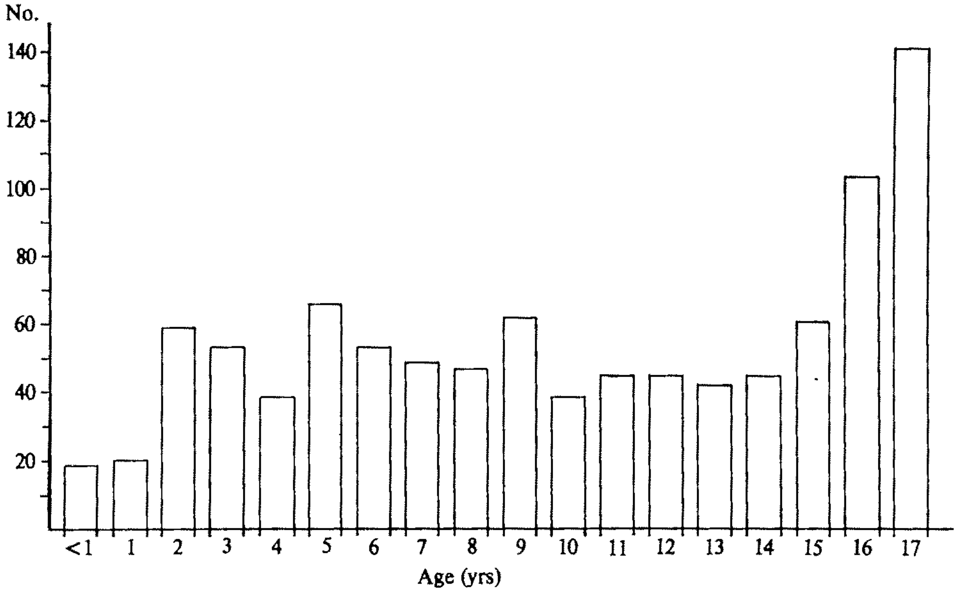

FIG. 2. Age distribution of 962 consecutive head-injured children, aged 2 months to 17 years.

TABLE 1. ABBREVIATED INJURY SCALE

Description of injury	*AIS code*	*Degree of injury*
Cerebral injury with headache; dizziness; no loss of consciousness.	1	Minor
Cerebral injury with or without skull fracture, with less than 15 min unconsciousness; undisplaced skull fracture; no post-traumatic amnesia.	2	Moderate
Cerebral injury with or without skull fracture, with unconsciousness more than 15 min, without severe neurological signs; brief PTA* (less than 3 h).	3	Severe (not life threatening)
Cerebral injury with or without skull fracture, with unconsciousness of more than 15 min with definite neurological signs; PTA 3–12 h. Compound skull fracture.	4	Severe (life threatening; survival probable)
Cerebral injury with or without skull fracture with unconsciousness of more than 24 h; PTA > 12 h; intracranial haemorrhage; signs of raised intracranial pressure.	5	Critical (survival uncertain)

*PTA = post-traumatic amnesia.

with a history of a brief loss of consciousness (not exceeding 5 min) followed by a lucid period, were included, bringing the total number to 42 (4.37 per cent of all patients). Forty of the patients were admitted immediately after the first neurological assessment, 2 had been allowed to go home, one of whom was subsequently admitted on the same day. In one patient the (short) transient period of deterioration had occurred several hours previously and at the time of neurological examination this patient had no symptoms; he therefore was allowed to go home. Fig. 3 shows the age distribution of the 42 patients. The patients were divided into two categories (fig. 4), the criterion being the occurrence or absence of convulsions (Oka *et al.*, 1977).

Group 1. Convulsive Cases

Thirteen children (31 per cent) had early post-traumatic seizures, occurring in the first week after injury (Jennett, 1962, 1969, 1975). Table 2 presents the characteristics of this group. Seven patients developed a focal or generalized status epilepticus, which necessitated intubation and controlled ventilation in 6. More than half of the patients developed these seizures within one hour after injury, 12 out of 13 within two hours, and only one after a longer period (28 h).

Case 1. A 5-year-old-boy fell off his bicycle. He did not lose consciousness and resumed cycling immediately. One hour after injury he developed focal seizures involving the right hand and arm. On admission one hour later, the boy was in generalized status epilepticus, which reacted promptly to intravenous diazepam. A CT scan performed within three hours after injury showed no abnormalities. The mean CT attenuation numbers of the deep frontal white matter were 15.9 EMI units (SD 2.59).

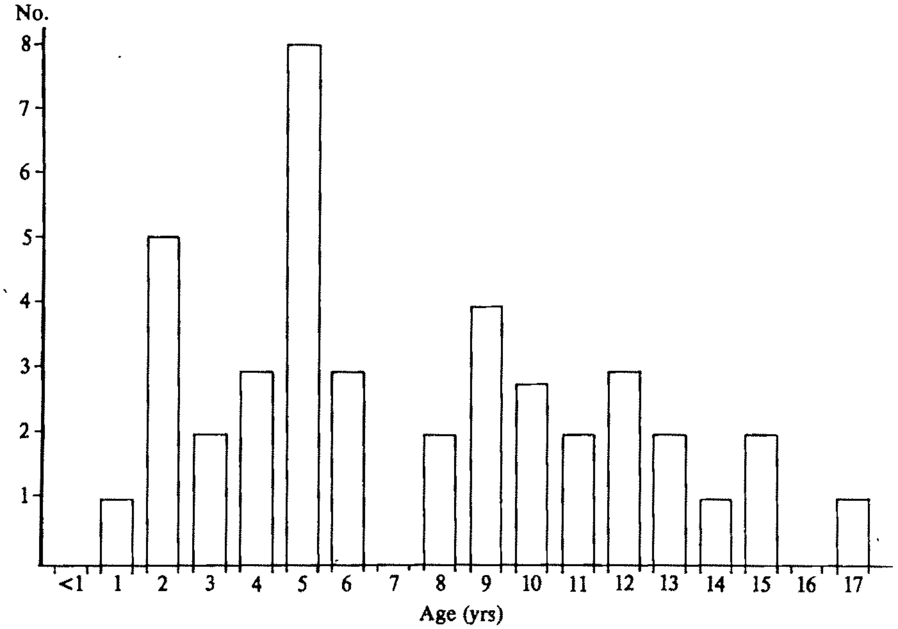

FIG. 3. Age distribution of 42 children with a lucid interval following mild head injury.

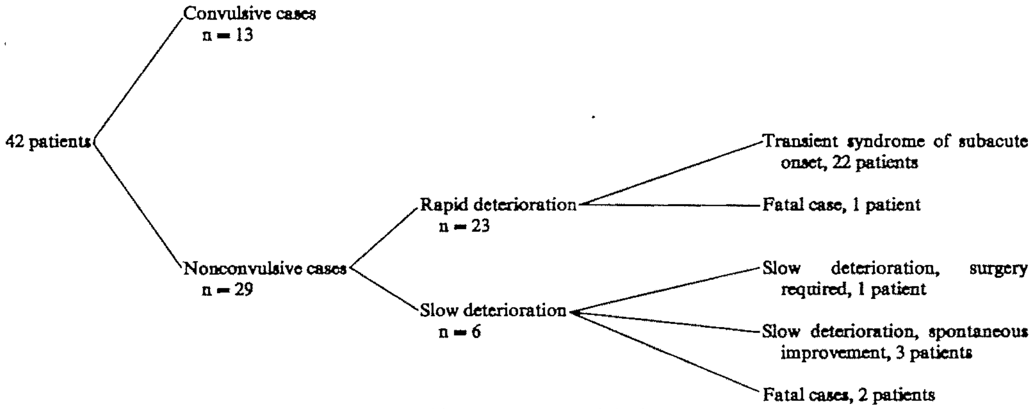
Convulsive cases
n = 13
42 patients
Nonconvulsive cases
n = 29
Rapid deterioration
n = 23
Slow deterioration
n = 6
Transient syndrome of subacute onset, 22 patients
Fatal case, 1 patient
Slow deterioration, surgery required, 1 patient
Slow deterioration, spontaneous improvement, 3 patients
Fatal cases, 2 patients

FIG. 4. Lucid interval series. Clinical course.

TABLE 2. CHARACTERISTICS OF CONVULSIVE CASES

Number: 13
Mean age: 7.3 years (range 1–17)
Cause of injury: fall, 10
traffic accident, 1
struck by object, 2
Skull fracture: 5 (38 per cent)
Onset after injury: within 1 h, 7 (54 per cent)
within 2 h, 12 (92 per cent)
Vomiting at onset: 3 (23 per cent)
Types of seizures: partial seizures, 4
partial + generalized seizures, 5
generalized seizures, 4
Status epilepticus: 7 (54 per cent)
Mean age of patients with status: 3.5 years (range 1–8)
Family history of epilepsy: 0
Past medical history: febrile convulsions, 1
rhesus incompatibility, 1
prematurity, 1
mental retardation, 1
early post-traumatic epilepsy, 1
Late epilepsy (follow-up 6 months to 3 years): 1

The ventricles were small, but the basal cisterns appeared normal. An EEG, performed within 24 h, showed asymmetry with localized slow activity in the left temporal region. There were multifocal isolated spikes and sharp-slow wave complexes, maximal in both temporal and parietal areas.

Several hours after admission the patient was fully alert, recalling all details of the injury. He was discharged after two days. Two EEGs, performed one and five months after injury, respectively, were normal. The past medical history of this patient revealed that he was premature and dysmature at birth. During the first fourteen days of life cyanosis had been seen on several occasions. Serial EEGs had not shown any abnormality at that time. He had been treated with anticonvulsants up to the age of five. Psychomotor development was normal.

The family history for epilepsy was negative in all patients. Five patients, however, had a past medical history (febrile convulsions, rhesus incompatibility, mental retardation or prematurity; 1 patient had had an identical episode of

TABLE 3. RELATION OF EEG ABNORMALITIES TO TYPE OF SEIZURE

	EEG					
Type of seizure	*N*	*D*	*F*	*D+F*	*E*	*F+E*
P	1		2	1		
P+G		1		1		2
G			1	1	1	

Type of seizure. P = partial seizure. PG = partial + generalized seizure. G = generalized seizure.
EEG. N = no abnormalities. D = diffuse abnormalities. F = focal abnormalities. E = epileptic discharges.

convulsions after a previous trivial injury). One patient possibly had a rubella infection and was readmitted with a second episode of status epilepticus a week later at which time an increased rubella titre was found. Apart from this patient no recurrence of seizures was noted in the follow-up period (six months to three years).

One or more EEGs were performed in 11 cases, usually within 24 h after injury (range 6 h to 9 days). Table 3 shows that there was no relation between the EEG findings and the type of seizure.

In only 2 patients was CT performed immediately following the convulsions. Both were normal. The densities measured in the deep frontal white matter were 15.9 EMI units, SD 2.59 (Case 1) and 11.3 EMI units, SD 1.60, respectively.

Group 2. Nonconvulsive Cases

These 29 children did not develop early post-traumatic seizures. In the majority (23 cases), there was a history of acute or subacute deterioration (i.e. from a level of no signs, the full clinical picture was reached within 15 min) at varying times after injury, whereas in the remaining 6 cases there was a slow, gradual deterioration.

Cases with rapid deterioration. A. Patients with a transient syndrome of acute or subacute onset. Patients were included in this group if the following criteria were met. (1) Acute or subacute onset. (2) Signs ending quickly, sometimes abruptly, mostly after a short period (not exceeding 12 h). (3) Nature of signs: loss of consciousness with or without focal neurological signs, focal neurological signs only or a period of severe restlessness or confusion following a period of normal behaviour.

This subgroup consists of 22 patients whose characteristics are listed in Table 4.

TABLE 4. CHARACTERISTICS OF NONCONVULSIVE CASES WITH A TRANSIENT SYNDROME OF ACUTE OR SUBACUTE ONSET

Number: 22
Mean age: 6 years (range 2–13)
Cause of injury: fall, 15
    traffic accident, 5
    struck by object, 2
Skull fracture: 5 (23 per cent)
Onset after injury: 5–30 min, 12
    30–60 min, 4
    1–2 h, 5
    36 h, 1
Duration of signs: 15–30 min, 5
    30 min–2 h, 2
    2–12 h, 15
Vomiting at onset: 21 (95 per cent)
Signs: disturbances of sensory level only, 7
    disturbances of sensory level with focal neurological signs, 9
    focal neurological signs only, 1
    confusion, 5

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The past medical history was unremarkable in all but 3 cases. One girl (aged 12 years) was known to have behavioural problems and EEG abnormalities (bilateral synchronous spike and wave complexes) without history of seizures. One boy (aged 5 years) had had febrile convulsions in the past. There was a family history of epilepsy but no history of seizures in another boy (aged 6 years), whose EEG subsequently showed spike and wave complexes. One patient was admitted with fever, the CSF showing no abnormalities.

There were remarkable differences in the severity of the presenting clinical picture as is illustrated by the following case histories.

Case 2. A 2-year-old boy fell down some stairs. He cried immediately. One hour later he became unresponsive within a few minutes. On admission he was obtunded with a left hemiparesis. A CT scan, performed within three hours of injury, was normal, with frontal white matter attenuation values of 11.7 EMI units, SD 1.57. Within four hours after the injury the hemiparesis disappeared and the level of consciousness became normal. Two days later the boy was discharged. An EEG, performed on the same day, showed slow waves over the whole of the right hemisphere.

Case 3. A 5-year-old boy was struck by a car. He was unconscious for less than five minutes. In the ambulance the right pupil dilated while he was talking. He subsequently became comatose with bilaterally dilated unreactive pupils. On admission, one hour after the accident, he was awake with normally reacting pupils. The EEG (day 5) showed only slight diffuse abnormalities. He was discharged after six days.

A similar short-lasting but alarming picture, consisting of deep coma with bilaterally unreactive pupils, resembling acute tentorial herniation by a rapidly expanding mass, was seen in one other patient in this group, a girl aged 12 years. In this patient these signs occurred 36 h after injury. The CT scan performed at that time showed small ventricles with obliterated cisterns (fig. 5). The deep frontal white matter densities were 17.4 EMI units, SD 2.47.

The most frequently observed focal neurological signs were pupillary abnormalities (in 4 out of 10 patients), followed by conjugate eye deviation and hemiparesis. A combination of focal signs was seen in 2 children. Two patients presented with transient blindness. In both patients the onset of blindness (some minutes and one hour after injury, respectively) occurred in combination with sudden vomiting. The period of blindness lasted less than one hour in both cases and ended abruptly. One child had struck his forehead, the other had fallen on his occiput.

In this group of patients, 6 EEGs were performed within one to five days after injury. Three of these showed local slow activity, 1 slight diffuse abnormalities, whereas bilateral synchronous sharp and slow wave complexes were noted in 2. A CT scan was performed in only 2 cases (*presented above*).

B. *Fatal case with a rapid deterioration. Case 4.* An 8-year-old boy jumped from a slowly moving cart and fell on his head. He got up immediately, walked towards his father and said 'I feel so funny in my head'. He then became flaccid. His mother, a nurse, subsequently stated that she had noticed dilated pupils at the time. On admission one hour later the boy was shocked and respiration was shallow. He was unresponsive and both pupils were dilated and fixed. No bruises were found on the head and there was no skull fracture. Echoencephalography showed no midline shift. The boy was intubated and ventilated. Soon after admission massive pulmonary oedema developed. It was felt that the situation was hopeless and no attempts were made at further investigation. He died within hours of admission. Permission for donor nephrectomy was granted by his parents; no attempts were made to obtain permission for autopsy.

Slow deterioration. A. *Slow deterioration, treated surgically. Case 5.* A 10-year-old boy struck his head against a wall while being tossed by his friends. He was briefly unconscious, probably less than one minute, but recovered quickly. On admission he opened his eyes on request, obeyed commands and was fully orientated. There was a small occipital fracture. He deteriorated slowly over the following day. Laboratory screening revealed a clotting disorder, which was found to be a variant of von Willebrand-Jürgens disease. A CT scan showed a hyperdense area in the posterior fossa, which on exploration proved to be an extradural haematoma. He made a slow but excellent recovery.

B. *Slow deterioration with gradual spontaneous improvement.* In 3 patients (aged 10, 12 and 15 years, respectively) the signs developed slowly over a period of time after a lucid interval and then gradually resolved. In 2 patients these symptoms consisted of slowly progressive confusion with focal abnormalities in both the EEG and CT scan, located in the frontal region in one patient and in the left temporal region in the other. In the third case (Case 6) the deterioration consisted of more severe confusion, with signs of uncal herniation.

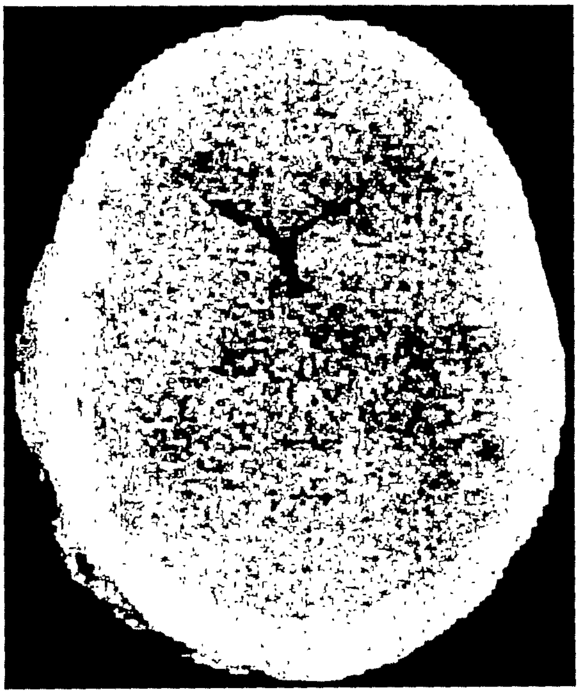

FIG. 5. Example of CT section at the level of the anterior horns and the mesencephalon. Note the narrow aspect of the ventricular horns which are not significantly displaced from the midline. The CSF cistern behind the quadrigeminal plate is obliterated.

Case 6. A boy aged 12 years was hit by a car. He did not lose consciousness. On admission he was lucid but nauseated. There was no skull fracture. Twelve hours after the accident he started to deteriorate with confusion and an enlarged pupil on the right. Angiography (because of unavailability of our CT scanner) showed a shift of the midline vessels with signs of a swollen right temporal lobe. No avascular mass was discovered. Several hours later his level of consciousness started to improve and the pupils became normal. The boy remained drowsy for two more days after which he recovered quickly. An EEG performed four days after injury showed diffuse slowing together with a local area of slow activity in the right temporal region.

C. *Fatal cases with slow deterioration. Case 7.* A 13-year-old girl fell off her bicycle. She did not lose consciousness at the time. On examination, three hours after the accident, she was lucid but nauseated. No neurological abnormalities were found. There was no skull fracture. She was sent home. Several hours later she developed a left hemiparesis and became drowsy. She was admitted to our hospital. A CT scan showed a marked shift of the compressed ventricles to the left. No abnormalities in the brain parenchyma were detected. Unfortunately raw CT data are no longer available, so no frontal white matter attenuation values can be measured in retrospect. An angiogram, performed in order to exclude an isodense haematoma, showed slowed intracerebral circulation, but no avascular mass. The girl was intubated and ventilated; high doses of corticosteroids were given, together with mannitol. She deteriorated over the next few hours and died on the following day. Autopsy was not performed.

Case 8. A boy aged 9 years fell off his skateboard. He resumed playing immediately, not having lost consciousness. Later that day he watched television for several hours and then went to bed. The next morning he complained of a headache and told his mother that he had difficulty in walking. Some time later he became stuporose and vomited. On admission, 16 hours after the accident, he did not open his eyes to painful stimuli, but he located these adequately while moaning. A bruise was noted in the right parietal area. There was no skull fracture. The left pupil was dilated, the right pupil somewhat smaller; neither reacted to light. While the patient was being examined both pupils started to react to light spontaneously. As the CT scanner was not available, an angiogram had been scheduled. It was felt, however, that the spontaneous improvement made an expanding intracranial mass less likely. Without having further deteriorated in the meantime, the boy suddenly developed fixed dilated pupils and apnoea. He was immediately taken to the operating theatre where bilateral burr holes revealed a swollen brain but no haematoma. The boy died 15 hours after admission. Consent for autopsy was refused.

DISCUSSION

The largest series of head-injured children, 4465 consecutively admitted cases, was reported by Hendrick *et al.* (1964). It was shown that almost 50 per cent of those who died were not in coma at the time of admission to hospital. Also, a history of a short or prolonged lucid period was present in 0.8 per cent of the patients, whereas the level of consciousness deteriorated gradually from the moment of impact in 1.8 per cent. Only the last category was correlated with a high percentage of intracranial, mostly extradural, haematomas.

In this study we assessed children who, following a minor or trivial injury, developed neurological signs following a lucid or symptom-free period. As these included cases with focal neurological signs in conscious children and early post-traumatic convulsions not leading to coma, it is not possible, strictly speaking, to use the term 'lucid interval', which refers to level of consciousness only, in these cases.

Therefore the criterion 'symptom-free' has been added. It does not seem illogical to use these criteria because in this way it is possible to focus attention on all those patients who demonstrated disturbed cerebral function after an injury which at first had appeared to be minor or even trivial.

In 4.37 per cent of 962 patients such a symptom-free period was encountered. In only one of these patients was an intracranial haematoma subsequently found. The remaining 41 patients showed a syndrome consisting of either convulsive or nonconvulsive signs.

Post-traumatic Epilepsy

Early post-traumatic epilepsy was noted in 16 head-injured children (1.6 per cent of our total series of 962). The 3 patients not having had a lucid interval all had a depressed fracture (fig. 1). According to Jennett (1962, 1973, 1975), early post-traumatic epilepsy is seen in about 5 per cent of all head-injured patients admitted to hospital. In children under 5 years of age, however, the incidence is twice as high. Hendrick and Harris (1968) also give an incidence of about 10 per cent in this age group. In patients under 5 years of age we found a percentage of 3.2 per cent. The difference between the incidence found by Jennett and by Hendrick and Harris, and by us, probably reflects the distinction between patient populations in neurosurgical and neurological departments.

According to Jennett, epilepsy rarely follows a trivial injury except in children under 5 years. The only adults encountered with epilepsy after trivial injury are those with 'immediate' epilepsy, when a seizure occurs at the moment the head sustains an impact. In the present series, the occurrence of early post-traumatic epilepsy was not limited to the under 5 age group, as 6 of the 13 patients were between 6 and 17 years of age. A similar age distribution has been described by Grand (1974).

Two explanations are possible for the relatively high frequency of early post-traumatic epilepsy following trauma in children as compared to adults (Jennett, 1962, 1975). The first is that children are predisposed to epilepsy, related to underlying but hitherto undetected brain damage. The second, favoured by Jennett and by Oka *et al.* (1977), is that children are somehow more liable to react to stress of different kinds by a seizure. Our finding that in almost half of the convulsive cases there was, albeit ill defined, a past medical history (*see* Table 2), which may have resulted in a liability to develop convulsions, gives some support to the first possibility expressed by Jennett. According to this author, the major significance of early post-traumatic epilepsy is the risk of late epilepsy, which he found to be 25 per cent. Focal early epilepsy in children was the only kind of early epilepsy in his series which did not significantly increase the risk of late epilepsy. Except for the child that was readmitted in a second episode of status epilepticus one week after the accident, no other cases of late epilepsy were encountered during the follow-up (three months to three years) of our patients with early epilepsy following trivial injury (Table 2). Oka *et al.* (1977) did not find a single case of late epilepsy in their series.

In the literature several explanations have been offered for the delayed deterioration in children following minor injuries. Several authors considered both convulsive and nonconvulsive signs as part of one syndrome and have attempted to give an explanation for its occurrence (Biemond, 1970; Haas *et al.*, 1975; Oka *et al.*, 1977); others have confined themselves to giving an explanation for the occurrence of convulsions only (Livingston and Mahloudji, 1961) or of nonconvulsive signs only (Walton and Brooks, 1897; Pickles, 1949; Gjerris and Mellemgaard, 1969; Bruce *et al.*, 1979, 1981*a*, *b*; Todorow and Feller, 1982).

Spreading Depression of Leão

By dividing our patients into two groups, convulsive and nonconvulsive cases, we follow Oka *et al.* (1977). They described a series of 37 children in whom transient neurological disorders occurred in the acute stage of trivial head injury and for whom no surgical treatment was subsequently required. The ages of their patients ranged from 10 months to 21 years, but the majority were under 14 years of age. Of these 37 children, 28 developed convulsive attacks and 9 children demonstrated nonconvulsive signs following a head injury without initial loss of consciousness. As in our series, most of the convulsive patients were under 8 years of age. Our group of patients with a transient syndrome of subacute or acute onset (Table 4) shows the greatest resemblance to their group of nonconvulsive cases, although our patients tended to be younger. They considered the nonconvulsive signs to be the primary and basic disturbance and they regarded the convulsive attacks as secondary phenomena. According to these authors, both phenomena can be explained as manifestations of the experimental phenomenon designated as spreading depression of Leão. In rabbits, Leão (1944) found that weak faradic or mechanical stimulation of the exposed cerebral cortex elicits a characteristic response, consisting of a marked enduring reduction of the spontaneous electrical activity of the cortex. Typical discharges of experimental epilepsy were noted in cortical regions when these were reached by a spreading wave of depression. Oka *et al.* suggested that the fact that the nonconvulsive disturbance was followed by convulsions in the younger children could be ascribed to a maturational factor, but that the primary process, the spreading depression, was identical in both groups. Thus, according to these authors, only the age factor determines whether the syndrome of transient neurological disorders, which include headache, nausea and vomiting, pallor, somnolence, irritability and restlessness, stupor, hemiparesis and aphasia, is followed by convulsive attacks. We noted some differences between our convulsive and nonconvulsive patients, however, which may indicate that the two phenomena are not as closely linked as these authors suggest. First there was, as stated earlier, a past medical history in almost half of the convulsive patients, which may have resulted in a liability to develop convulsions. Secondly, although a nonspecific sign such as vomiting was noted at the onset of the deterioration of almost all patients in the nonconvulsive group (Table 4), this sign was only rarely seen in patients with early post-traumatic convulsions (Table 2). We were unable to confirm the finding of Oka *et al.* (1977) that the convulsive attacks did not develop directly from a lucid interval, but were nearly always preceded by nonconvulsive signs to a greater or lesser degree.

A Migrainous Mechanism

Haas *et al.* (1975), in a study of 25 patients, described 50 attacks consisting of transient neurological signs following mild head trauma; 40 of the attacks occurred in children under 14 years of age. All attacks developed after a latent interval, generally of one to ten minutes. Attacks were grouped into 4 clinical types: (1) hemiparesis; (2) somnolence, irritability and vomiting; (3) blindness and (4) brainstem signs. Two patients had an epileptic seizure. Five of the children later had spontaneous attacks which resembled their triggered attacks closely enough to be considered the same experience. The authors concluded that the temporary post-traumatic syndromes mentioned by them can be seen as diverse manifestations of a common underlying process which involves the cerebral vasculature, and that they resemble spontaneous classical migraine attacks in juveniles closely enough to postulate an underlying mechanism similar to migraine. Several authors (*see* Oka *et al.*, 1977; Shinohara *et al.*, 1979) regard this mechanism as analogous or identical with the mechanism underlying migraine.

A Functional Disturbance of the Rostral Brainstem

Todorow and Feller (1982) have recently described 49 children with mild post-traumatic stupor. This 'sleepy state', which lasted for 3 to 5 h, occurred in 9 per cent of all children admitted after a minor head injury. The lucid interval ranged from 15 min to 3 h. In almost one-third of the patients minor neurological signs were noted (pupillary abnormalities, pyramidal tract signs or ataxia), while EEG abnormalities were found in more than half. These EEG abnormalities mostly consisted of slight to moderate slowing of background frequency and, in many cases, persisted for a considerable time (from 5 days to 6 weeks) after the clinical signs had subsided. The authors postulate that both the secondary disturbance of consciousness and the EEG abnormalities can be explained by a functional disturbance of the rostral brain stem, probably related to the lability of arousal mechanisms in children.

In our series we have not regarded sleepiness in itself as a sign of secondary deterioration. Many children will fall asleep some time after the shock of an injury and the subsequent examination and treatment in an unfamiliar hospital setting. We cannot exclude the possibility, however, that the children in the Todorow and Feller series who became somnolent without developing focal neurological signs may represent the mildest form of the 'delayed deterioration syndrome'.

Direct Contusion of the Cerebral Cortex

Livingston and Mahloudji (1961) reported 4 patients between 2 and 4 years of age who developed convulsive seizures after a latent interval following mild head injury. They postulated that, since this picture has only been seen in young children at an age when the cranium is rather malleable, deformation of the cranium at the moment of impact produces direct contusion of the cortex.

Focal or Generalized Brain Swelling, Due either to Rapid Oedema Formation or to Cerebral Hyperaemia

For almost a century there have been reports of clinical findings in head-injured children and adolescents strongly suggesting the presence of a rapidly expanding intracranial haematoma, but with these findings apparently being due to some other condition. The first case reports were published by Walton (1898) and Walton and Brooks (1897).

Pickles (1949) concluded that transient acute cortical oedema, with associated capillary anaemia, best explained the rapid and complete recovery without operation. Biemond (1970) also considered rapid oedema formation to be the cause of the transient cortical dysfunction accompanied by loss of consciousness. He differentiated between the more common benign transient syndrome and the rare fatal cases, which he saw only three times during his long career. These three children died after an exploratory craniotomy yielding negative results. Post-mortem examination showed diffuse cerebral swelling with microscopic findings of hyperaemia in the smaller arteries and precapillaries. He concluded that there was evidence both of brain swelling and brain oedema and he considered the brain swelling to be the primary event, probably attributable to diencephalic lesions.

Lindenberg *et al.* (1955) described the post-mortem findings of children dying from blunt head injuries. Diffuse cerebral swelling was the most consistent finding. They concluded that this post-traumatic brain swelling is markedly more common in children than in adults and that it may develop after a seemingly minor head trauma without subsequent loss of consciousness. Similar findings have been recorded by other pathologists (Adams and Graham, 1972; Adams, 1975), who also reported that they could not find distinct abnormalities on histological examination.

Until recently, post-traumatic brain swelling has always been attributed to brain oedema, but the crucial evidence for this cause is lacking. According to Miller and Corales (1981), direct measurements of water content of the brain have not been reported in patients with head injury. The concept of brain oedema causing diffuse cerebral swelling has now been replaced by the alternative explanation of increased cerebral blood volume. Bruce *et al.* (1979, 1981*a*, *b*) and Zimmerman *et al.* (1978) described the CT appearance of diffuse cerebral swelling, which they considered to be the commonest CT finding in head-injured children. This CT picture consists of obliteration or narrowing of the lateral and third ventricles and perimesencephalic cisterns, while cerebral attenuation values are higher than on follow-up scans. According to these authors, these attenuation numbers (measured in the deep frontal white matter) are also higher than the normal range defined from values measured in normal paediatric CT scans and certainly higher than would be expected if brain oedema were the cause of this cerebral swelling, as an increase in water content of the brain is linearly related to a decrease in attenuation numbers.

The finding of increased cerebral blood flow (CBF) in the patients who showed this CT pattern of diffuse cerebral swelling is taken to suggest a relationship between the increased attenuation at CT, and this increased CBF and the cerebral swelling is therefore ascribed to cerebral hyperaemia. The association of diffuse cerebral swelling and hyperaemia has also been reported by Obrist *et al.* (1979) from the same institution. Cerebral metabolism studies in their hyperaemic patients yielded a very low oxygen uptake and arteriovenous oxygen difference, indicating that the high blood flow is a true 'luxury perfusion'. The cause of the cerebral vasodilatation, which allegedly leads to cerebral swelling, is as yet unknown. Meyer *et al.* (1971) found in their animal model that the areas which caused increases in CBF when stimulated were located in the pontine and midbrain reticular formation, the thalamus and the hypothalamus. Raichle *et al.* (1978) assumed that locus coeruleus stimulation may change both CBF and cerebral capillary permeability, probably through central vascular aminergic pathways. Recently, Mies *et al.* (1981), using autoradiographic techniques, observed an increase in cerebral blood flow during spreading depression in animals. This finding thus appears to link the theories of Bruce *et al.* (1979, 1981*a*, *b*) with those of Oka *et al.* (1977). The increase in CBF found by Mies *et al.* (1981), however, was linked with increased metabolism, which means that apparently the increase in CBF during spreading depression cannot be interpreted as 'luxury perfusion'.

There are some unresolved problems relating both to the CT appearance of diffuse cerebral swelling and to the theory ascribing this swelling to vascular engorgement. Until clearly defined criteria for minimal ventricular size in normal children are set, caution is needed in interpreting the sign of 'small ventricles' (Snoek *et al.*, 1979). The perimesencephalic cisterns are normally quite evident in children, but the same caution is needed in attaching any value to an alleged 'compression or narrowing'; in our opinion only clear absence of these cisterns on the CT scan warrants a conclusion of cerebral swelling.

The unresolved problems in the theory ascribing the CT picture of diffuse cerebral swelling to vascular engorgement are threefold. The first is the reliability of cerebral attentuation coefficients determined by CT. We feel that relatively small changes in CT attenuation numbers, as described by Zimmerman *et al.* (1978), should be interpreted with circumspection. We have attempted to reproduce the normal range of values established by these authors (14.6 to 16.6 EMI units in the deep frontal white matter of 18 normal hemispheres). We determined average attenuation numbers in the same fashion in circular fields of 150 to 350 pixels each in the deep frontal white matter of 6 hemispheres of children aged 1 to 12 years, in whom no signs of cerebral swelling could be found at CT. All the examinations had been performed on the same scanner (EMI 5005) using a 160 × 160 matrix, 10 or 13 mm slice thickness. In some subjects a scan time of 70 s per slice was selected, in others 20 s. The same variable scanning parameters were used in the other subjects whose CT characteristics are mentioned elsewhere in this study. In our 6 subjects white matter CT attenuation numbers ranged from a maximum average of 19.5 EMI units per measuring field (SD 2.42) to a minimum of 11.7 EMI units (SD 2.08). This is a much larger spread of normal values than is presented in the material of Zimmerman *et al.* (1978).

A number of factors may influence the assessment of tissue attenuation coefficients as expressed in CT numbers.

(1) *Scanner characteristics.* These vary from one manufacturer to another with regard to acquisition of data (scanner generation, presence or absence of a water bag), as well as the method of reconstruction. Extreme caution must be exercised in any comparison of different types of scanners often functioning under dissimilar operating conditions (Speller *et al.*, 1981). With regard to a single CT scanner, consistency of performance may be influenced by the state of maintenance (McCullough, 1977). The EMI 5005 whole body scanner mentioned in our study is serviced by contract with the manufacturer. It is also interesting to note that, as the linear attenuation coefficient of water decreases with increasing temperature, there is a difference in CT attenuation numbers of 2.5 to 3.0 EMI units between water at room temperature and water at body temperature. This should be taken into account in calibration of the scanner (Bydder and Kreel, 1979). Factors such as voxel size (determined by slice thickness and area represented by a pixel) may be expected to influence the statistical accuracy of the attenuation measurement. It is also our experience that in the EMI 5005 scanner CT attenuation numbers determined in a 20 s rapid scan are usually significantly higher than in a 70 s slow scan performed in the same region. We have no explanation for this discrepancy. Finally, changes in position of the head within the scanner ring can cause variations in CT numbers measured in the same cerebral region in serial examinations, as can changes in kilovoltage between examinations (Levi *et al.*, 1982).

(2) *Factors related to the patient.* The most important of these appears to be skull thickness. As the x-ray beam traverses tissue, its composition is altered. The lower-energy photons are filtered out, and while the x-ray beam as a whole is attenuated, the mean kinetic energy of the remaining photons is higher. This beam-hardening effect is especially marked in substances with a high linear attenuation coefficient such as bone, and when a large thickness of skull has to be traversed, this will influence attenuation measurement of skull contents (Di Chiro *et al.*, 1978). Shifts of some 7.5 EMI units have been noted between maximum and minimum skull thickness (Payne and Latchaw, 1978).

(3) *Partial volume effect.* Cerebral grey matter has a mean attenuation number some 3 EMI units higher than white matter (Weinstein *et al.*, 1977; Phelps *et al.*, 1975). If the field of measurement located in the frontal white matter should inadvertently contain grey matter, this will induce an upward bias in the mean CT attenuation value through a partial volume effect. This could happen if the field of measurement were located too near to the cerebral surface in the CT section, but also if a CT section were selected for measurement which contains in its basal portion some of the frontobasal grey matter.

The minor increase in CT attenuation number of 1.6 EMI units described by

Zimmerman *et al.* (1978) in their group of patients with post-traumatic brain swelling achieves statistical significance when serial measurements are performed in the same patient using the same CT scanner under identical operating conditions. We would like to warn, however, against attributing diagnostic significance to marginal variations in mean CT attenuation numbers measured in the first CT examination in an individual patient.

The second unresolved problem in relating the CT picture of diffuse cerebral swelling to hyperaemia is as follows. Although the increase of 1.6 EMI units in ET attenuation numbers mentioned above is relatively small in the context of other variable factors influencing the measurements, it represents a large shift if it is to be explained solely on the basis of increase in blood content. The blood concentration of cerebral white matter is reported to be 2.2 per cent and of grey matter 5.6 per cent (Ladurner, 1978). The CT number for blood is given as 27 EMI units (New and Scott, 1975), and for subfrontal white matter as 16.5 EMI units (Arimitsu *et al.*, 1977). In order to cause an increase of the value for white matter in the order of 1.6 EMI units, its blood content would have to increase very substantially. By the same token doubling the cerebral blood volume would result in an increase in total cerebral volume of only 3.5 per cent, and an increase of this amount of blood volume is hardly ever seen (Raichle, 1979).

The third unresolved problem is that the crucial measurement is cerebral blood *volume* rather than cerebral blood *flow*, as measured by Bruce *et al.* (Miller and Corales, 1981). Determination of cerebral blood volume (CBV) by emission tomography in 4 head-injured children belonging to the series of Bruce *et al.* (1981*a*) failed to demonstrate an increase in CBV in 3 of them (Kuhl *et al.*, 1980). These authors state that the CT pattern characteristic of diffuse brain swelling may occur in head-injured children without discernible increases in CBV and that this picture therefore cannot be explained by increases in CBV alone.

The clinical significance of the finding of a CT appearance suggesting diffuse cerebral swelling caused by cerebral hyperaemia is as yet unresolved. The crucial question is whether such a swelling (leading to severely increased intracranial pressure only in exceptional cases) is the *cause* of the deterioration in head-injured children or whether in most patients it is an epiphenomenon caused by the same processes which lead to the clinical deterioration. Cold and Jensen (1980) found that hyperaemia following head injury is a common phenomenon in children, that this hyperaemic phase lasts for some days to several weeks and that it is of no prognostic importance. The CT pattern of diffuse cerebral swelling is seen in 29 per cent of head-injured children and adolescents. There is a higher incidence in patients with a low score on the Glasgow Coma Score (41 per cent with a score of 8 or less) than in patients with a score greater than 8 (15 per cent) (Bruce *et al.*, 1981*a*). These authors do not specifically mention the rate of occurrence of this CT pattern in children with a lucid interval. Conversely, in the clinical description of their group of 63 juvenile patients with the CT pattern of diffuse cerebral swelling, 37 per cent had experienced some form of lucid interval. Within the latter group two subgroups are described. In a typical case of the first subgroup (8 cases) there was a lucid interval with a period of talking and complete consciousness from minutes to hours after injury, followed by the onset of vomiting, headache and frequently pallor and sweating, associated with decreased alertness. These patients exhibited evidence of decreased spontaneous motor activity, and loss of spontaneous speech and eye opening. No mention is made of focal neurological signs. None of these patients progressed to coma according to the criteria of Teasdale and Jennett (1974) and the intracranial pressure when measured in these patients remained normal. All these patients made a good recovery. The other subgroup consisted of 15 patients who were unconscious following trauma and then had an interval associated with recovery of eye opening, occasional words and more spontaneous motor function. This was followed by rapid deterioration leading to coma (Glasgow Coma Score of less than 8). One of these patients died as a result of delayed brain swelling. The others all made a good recovery. The patients of our series are by definition only comparable with their first group of patients. As most of our patients showed a benign, often shortlasting syndrome, few CT scans were made. In only one out of 4 scans, performed in children with a rapid deterioration consisting of either convulsive or nonconvulsive signs, was the typical CT appearance consistent with diffuse cerebral swelling seen (fig. 5), which leads us to the conclusion that in the majority of cases deterioration apparently is not associated with such cerebral swelling and that, therefore, there must be other explanations for this rapid deterioration.

The CT scan of Case 7, a girl with a slow deterioration, was consistent with swelling of one hemisphere, a finding which has been described in CT scans performed in the period immediately after injury (Kobrine *et al.*, 1977; Waga *et al.*, 1979). In both cases this swelling was, on the basis of attenuation measurements, also attributed to vasodilatation and not to oedema. The results of the angiogram in our Case 6, also a child with a slow deterioration, support the interpretation that local damage can be followed by local swelling, associated with clinical deterioration. The clinical course, radiological and (in one case) surgical findings in our fatal cases, although not confirmed by autopsy, strongly suggest that 'malignant brain swelling' following trivial head injury in children does exist. Excluding the rare occurrence of intracranial haematoma, we feel, however, that the syndrome of delayed deterioration following mild head injury in children in fact covers a variety of pathological states and that neither the clinical nor the CT findings support the view that brain swelling caused by cerebral hyperaemia is the only or even the usual underlying cause for such deterioration.

We conclude that trivial injuries in children are not infrequently followed by a deterioration which is preceded by a lucid or symptom-free period and which is usually transient. It is very likely that only in a minority of affected children signs of such severity occur that these children will come under medical care. On clinical grounds it is possible to differentiate between several distinct pictures. At this moment it can only be speculated whether or not the different clinical pictures presented by these patients reflect different pathophysiological entities. With the exclusion of the relatively rare extracerebral haematoma, these clinical pictures point either to focal or generalized cerebral dysfunction, both with and without seizures. Although the recent theories developed by Bruce *et al.* relate the occurrence of cerebral dysfunction with diffuse cerebral swelling to hyperaemia, insufficient data are available so far to discriminate between this swelling being a causative factor for the deterioration or just an epiphenomenon in the majority of cases. We feel that caution is needed in interpreting the findings of marginally increased attenuation values in CT scans with small ventricles and compressed perimesencephalic cisterns as a state of diffuse cerebral hyperaemia and also in basing a therapeutic regimen solely on this interpretation. The rarity of this CT pattern in our patients does not give support to the assumption that in the majority of children diffuse cerebral swelling was the cause of the transient deterioration. There is now some evidence, however, that for unknown reasons some patients develop severe and often uncontrollable unilateral or diffuse brain swelling, as indicated by the radiological and surgical evidence in 2 out of our 3 fatal cases.

The fact that not infrequently deterioration following a trivial head injury may occur in children makes it mandatory in our opinion to accept a rather strict admission policy for head-injured children, especially if there is an indication in the past medical history that cerebral damage has been suffered in earlier life. In a deteriorating head-injured child that was symptomless before, the possibility of an expanding intracranial mass will always have to be excluded, preferably by CT scanning, although few haematomas will be found. The remaining patients usually show a benign and shortlasting syndrome followed by a spontaneous and full recovery in most, but not in all cases.

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DISORDERS OF PERCEIVED AUDITORY LATERALIZATION AFTER LESIONS OF THE RIGHT HEMISPHERE

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SUMMARY

The disorders of perceived auditory lateralization after unilateral damage of the cerebral hemispheres were investigated by dichotic presentation of pure tones, lateralization being obtained by interaural intensity differences. Observations were made on 107 unilateral brain-damaged patients and 30 normal subjects who were required to localize the perceived position of fused sound images. The images were generated by dichotic stimuli delivered through headphones and the patients were asked to point the perceived position.

A clear-cut hemispheric asymmetry was found. Whereas left brain-damaged patients and right brain-damaged patients without visual field defects were not impaired in this task in comparison with controls, the performance of right brain-damaged patients with visual field defects was defective, with a systematic directional error towards the right side, that is, the side ipsilateral to the damaged hemisphere. The defect of auditory lateralization involved both the half-space contralateral to the lesion and the ipsilateral one.

Different hypotheses are discussed in order to explain the present results. It is argued that they cannot easily be interpreted in terms of defective processing of sensory information and the proposal is made that lesions of the right hemisphere may produce a distortion of the internal representation of egocentric space to the right, yielding a systematic error of auditory lateralization. The site and the extent of the right hemisphere lesions producing the disorder of auditory lateralization are discussed.

INTRODUCTION

The disorders of auditory perception involving spatial analysis (that is, *localization* of sounds in the environment and *lateralization* of sounds fed into both ears from separate channels) after unilateral damage of the cerebral hemispheres in humans are a controversial issue.

Some studies have employed free-field dichotic methods: the sounds to be localized were delivered through loudspeakers, the patient being required to point to the sound source. Sanchez-Longo and Forster (1958) reported that only lesions that include one or the other temporal lobe affect auditory localization and that the impairment is confined to the half-space contralateral to the damaged hemisphere;

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no systematic directional errors (SDEs) were mentioned. Similar findings were later described by Klingon and Bontecou (1966), who observed, however, that extratemporal damage may also impair auditory localization; furthermore, they found that mislocalization is more frequently associated with right-sided brain damage, but did not comment upon this hemispheric difference. The finding that unilateral lesions impair contralateral localization is consistent with evidence from single case studies (Wortis and Pfeffer, 1948; Strominger and Neff, cited by Neff, 1968). Ruff *et al.* (1981) reported that lesions of the posterior regions of the right hemisphere, as compared with right anterior damage and with lesions of the left hemisphere, produce a greater impairment of auditory localization both in the contralateral and in the ipsilateral half-space; according to these authors SDEs do not occur. Negative results are also on record: Shankweiler (1961) was unable to find a significant defect of auditory localization after unilateral lesions, although right hemisphere-damaged patients showed a greater mean error. The possibility that the greater impairment of right brain-damaged patients might be due to a reaching disorder was ruled out in Shankweiler's experiment as similar results were obtained both when pointing was required and when the patient had to give a verbal response.

Other investigators using dichotic methods delivered the stimuli through earphones. In dichotic listening lateralization is obtained either by interaural intensity differences (ΔI) or by interaural time differences (Δt): the fused sound image is perceived as lateralized towards the ear which receives the more intense or leading stimulus. Studying lateralization by means of Δt, Matzker (1959) found an SDE towards the side ipsilateral to the lesion in two left and one right hemisphere-damaged patients, without left-right asymmetries. On the other hand, Walsh (1957) failed to detect any disorder by Δt in patients with unilateral hemispheric lesions. Teuber and Diamond (1956, cited by Teuber, 1962) reported that the performance of right brain-damaged patients is inferior to that of left brain-damaged patients, both groups being impaired in comparison with controls. These authors used both Δt and ΔI: only the latter produced an SDE towards the side ipsilateral to the damaged hemisphere. Altman *et al.* (1979) investigated auditory lateralization by Δt in 96 psychiatric patients who underwent unilateral electroconvulsive therapy: only electroshocks to the right hemisphere were followed by a transient impairment of auditory lateralization with an SDE towards the right side, that is, the side ipsilateral to the affected hemisphere.

As to the interpretation of these results, Ruff *et al.* (1981) suggested a spatial nature for the disorder of auditory localization as 'right posterior lesions are classically associated with spatial deficits'. They offered a twofold argument to support the hypothesis of a spatial deficit different from unilateral neglect. First, the defect of auditory localization involves both half-spaces. Secondly, there is no relationship between the presence of auditory extinction (i.e., according to Ruff *et al.* (1981) unilateral auditory neglect) assessed by the clinical method of bilateral simultaneous stimulation and a particular pattern of localization errors (for example, a greater quantity of error in the contralateral half-space or a greater absolute error score). Altman *et al.* (1979), however, who reported visual neglect in some of their patients, concluded that the auditory and the visual disorders may be considered as different manifestations of unilateral neglect.

In recent years there has been evidence to the effect that unilateral neglect cannot be explained in terms of defective processing of sensory information. De Renzi *et al.* (1970) showed that patients with right posterior lesions fail to explore the contralateral half-space tactually by making use of the ipsilateral unaffected hand. Bisiach *et al.* (1979) reported that in these patients the processing of the left side of mentally reconstructed visual images is defective. Further, Bisiach *et al.* (1981) showed that such patients fail to describe the left half of recollected visual images accurately. These results have been interpreted in terms of impairment of the internal representation of the egocentric space. According to this interpretation, a defective lateralization of auditory stimuli in one half of the space might indeed be predicted in patients with unilateral neglect. This hypothesis was tested in the present experiment. Given the disagreement in the literature, however, as to the disorders of directional hearing after unilateral cerebral lesions, the study was not confined to right brain-damaged patients with unilateral neglect, but included also right brain-damaged patients without neglect and left brain-damaged patients. We used dichotic stimuli delivered through earphones; lateralization was obtained by interaural intensity differences.

MATERIALS AND METHODS

Subjects

A total of 107 patients admitted to our department were included in this study: all had clinical and instrumental evidence suggesting a lesion involving one cerebral hemisphere. Patients with history or evidence of bilateral damage and patients with mental deterioration or ear disease were excluded. This led to the exclusion of 4 left and 3 right brain-damaged patients. Three left brain-damaged aphasic patients with visual field defects were not tested, due to their grossly impaired comprehension. Ninety-six patients had a cerebrovascular lesion; 11 patients had a cerebral tumour. According to the side of the lesion and the presence of visual field defects detected on confrontation, the patients were subdivided into four groups: 41 left brain-damaged patients without visual field defect (L−); 10 left brain-damaged patients with visual field defect (L+); 31 right brain-damaged patients without visual field defect (R−); 25 right brain-damaged patients with visual field defect (R+). Thirty patients admitted for diseases involving the nervous system below the midthoracic level served as control subjects (C). All subjects were right-handed on the Edinburgh Handedness Inventory (Oldfield, 1971). The 25 R+ patients were further subdivided into two subgroups according to their behaviour in a task requiring the crossing out of circles symmetrically arranged around a central circle (Bisiach *et al.*, 1979). Patients who omitted to cross out one or more left-sided circles were considered to show signs of contralateral neglect. Left brain-damaged patients and R− patients showed no impairment on this task. Fifteen out of 25 R+ patients displayed neglect, as assessed by the cancellation task.

Stimuli and Procedure

The stimuli were 1000 Hz pure tones, 2 s in duration, delivered *via* headphones. Nine dichotic stimuli with different interaural ΔIs were used: in four conditions the right ear stimulus was more intense than the left, in another four the reverse, and in one the two ears received equally intense stimulation. There were two further conditions in which either ear received monaural stimulation. The intensity of the monaural stimulus was 98 dB SPL (Sound Pressure Level). The intensities of the dichotic stimuli were as follows: 96-74 ($\Delta I = 22$ dB SPL), 96-82 ($\Delta I = 14$ dB SPL), 94-86 ($\Delta I = 8$ dB SPL), 92-88 ($\Delta I = 4$ dB SPL), 91-91 ($\Delta I = 0$ dB SPL). Subjects received instructions to report their perceptions of location of the acoustic image by pointing with their forefinger to the skull in the coronal plane passing through the ears. Brain-damaged patients used the unaffected hand, that is, the hand ipsilateral to the damaged hemisphere; half of the controls used their right hand and half their left.

A score was computed with reference to the midline localization of the acoustic image, which scored 0 deg. Lateralization of the sound image, as pointed out on the skull, scored 15 to 90 deg in 15 deg steps, 90 deg being lateralization at either ear. A positive score ($+15°$ to $+90°$) was given to lateralization to the right, a negative score ($-15°$ to $-90°$) to lateralization to the left. Three trials were given for each of the 11 stimulus conditions. The 33 trials were set in a fixed random order.

Statistical Procedures

A multivariate analysis of variance was carried out on the means of the five groups (C, L−, L+, R−, R+). After the multivariate analysis, multiple comparisons between variables were made in order to specify at which of the 11 stimulus conditions the scores differed in the four groups of brain-damaged patients. The differences between each of the four groups constituted the hypotheses of the experiment. The error rate was considered 'per hypothesis' but within each hypothesis we adopted a significance level that enabled us to carry out all the comparisons between variables with a known overall risk of type 1 error. The multiple comparison method yields theta values which must be compared with the upper percentage of the generalized beta distribution.

A second multivariate analysis concerned the means of the R+ patients, subdivided into two subgroups, on the basis of the presence (N+)/absence (N−) of unilateral neglect as assessed by the cancellation task.

RESULTS

Fig. 1 shows the performance of the five experimental groups. Left brain-damaged patients and R− patients behaved as the control subjects. Lateralization occurred towards the side which received the more intense stimulus. The greater was the interaural ΔI, the more lateralized was the acoustic image; monaural stimuli yielded maximal lateralization. Dichotic stimuli of equal intensity were localized on the midline. Conversely, the R+ patients made a systematic directional error (SDE), displacing the sound image towards the side ipsilateral to the damaged hemisphere. No omission errors were shown, namely, none of the patients failed to detect any of the stimuli.

The statistical analysis showed that the effects of cerebral damage ($F = 3.99$; df = 11, 122; $P < 0.0001$), of the side of the damage ($F = 8.53$; df = 11, 122; $P < 0.0001$) and of the presence of visual field defect ($F = 4.85$; df = 11, 122; $P < 0.0001$) were all significant. The interaction between the side of the hemispheric damage and the presence of a visual field defect was also significant ($F = 4.31$; df = 11, 122; $P < 0.0001$).

Multiple comparisons revealed significant differences only between the R+ patients and the L−, L+ and R− patients in the stimulus conditions shown in the Table. In all the remaining conditions the performance of the R+ patients did not differ significantly from that of the other three groups of patients. None of the comparisons between L−, L+ and R− reached significance level.

The possibility of these results being spurious because of the exclusion of aphasic patients has to be considered. In fact, only 3 aphasic subjects were unable to perform the experiment. Further, the L+ group included 2 global aphasics, 2 severe nonfluent aphasics, 5 severe fluent aphasics and 1 nonaphasic patient. This would appear to rule out the possibility of bias.

Fig. 2 shows the performance of the two R+ subgroups. Although the N+ patients showed a greater mean SDE, this trend did not reach significance level (F < 1; df = 11, 8; n.s.).

Further, two multivariate analyses of covariance (Anderson, 1958) were performed. The first concerned the means of the five groups adjusted for age and years of schooling. The second was carried out on the means of the four brain-damaged groups, which were also adjusted for two measures related to the cerebral damage,

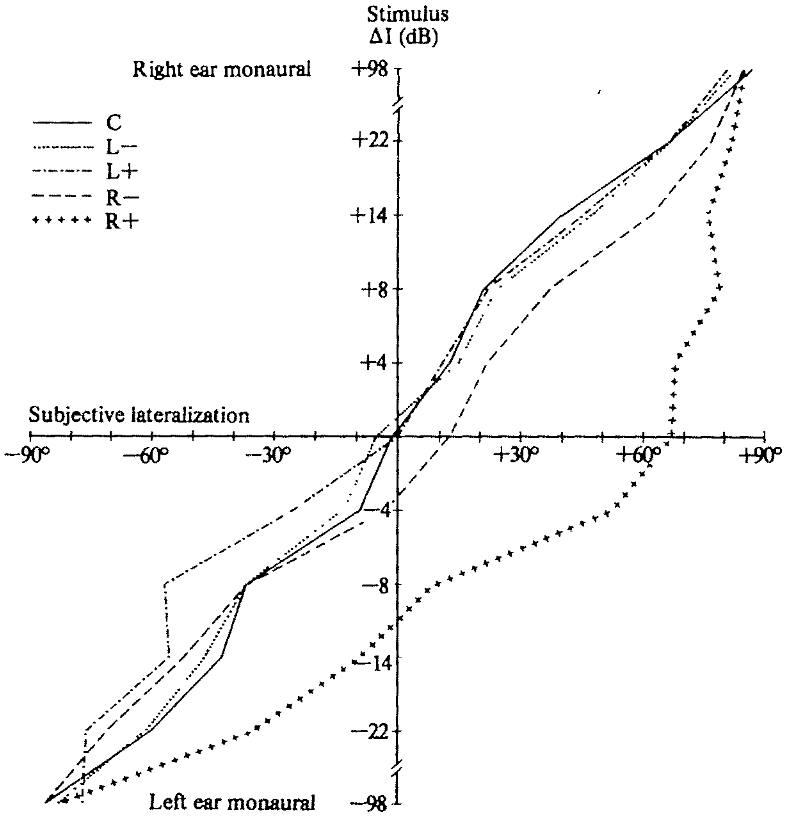

FIG. 1. Lateralization curves in the five experimental groups. *Ordinate*. ΔI: interaural intensity difference; positive values (+98 dB to +4 dB) right ear more intense; negative values (−4 dB to −98 dB) left ear more intense. *Abscissa*. Perceived lateralization; positive values (+15 to +90 deg): lateralization to right; negative values (−15 to −90 deg): lateralization to left. *Origin of the axes*. ΔI = 0 dB: midline localization.

TABLE. MULTIPLE COMPARISONS BETWEEN R+ PATIENTS AND L−, L+ AND R− PATIENTS

Stimulus conditions	*L−*	*L+*	*R−*
22 dB	n.s.	n.s.	n.s.
14 dB	0.15832*	n.s.	n.s.
8 dB	0.31587**	0.19405**	0.18546**
4 dB	0.33388**	0.21083**	0.25159**
0 dB	0.56665**	0.34152**	0.39611**
−4 dB	0.43666**	0.31710**	0.33669**
−8 dB	0.21251**	0.18081*	0.19717**
−14 dB	0.18560**	n.s.	0.19584**
−22 dB	n.s.	n.s.	0.17108*

Theta values with 1, 11 and 118 parameters according to Foster and Rees (1957). * Significant at the 0.05 level for theta = 0.14912. ** Significant at the 0.01 level for theta = 0.18344. All other comparisons were not significant.

namely, motor and somatosensory impairment score (Bisiach and Faglioni, 1974) and days which had elapsed since the onset of the disease. For the patients with a cerebral tumour the length of illness was arbitrarily scored as one day. These analyses showed that age, years of schooling, length of illness and the neurological disability score did not bring about significant adjustments.

Assessment of Hearing Function

The possibility that interaural intensity differences of hearing function might play a role in the disorders of auditory lateralization was considered. There is evidence that unilateral hemispheric lesions may produce contralateral hearing loss (Karp *et al.*, 1969).

The patients who could be moved to the Audiology Department underwent a pure tone air conduction audiometry in a sound-proof chamber. The 250, 500, 1000, 2000, 4000 and 8000 Hz frequencies were tested. Eleven L−, 6 L+, 13 R− and 13 R+ patients were examined. A multivariate analysis of variance was carried out on the interaural intensity differences of hearing loss in dB. The general analysis showed no significant differences between the four groups (F $<$ 1; df = 6, 34; n.s.).

As to the R+ group, at the 1000 Hz frequency 5 patients showed no interaural differences of hearing loss, 6 patients showed a greater left ear loss, 2 patients displayed a greater right ear loss. *Nevertheless all made an SDE to the right.* The R− group, where no disorders of lateralization were observed, stands comparison: 7 patients showed no interaural differences of hearing loss, 4 patients a greater left ear loss, 2 patients a greater right ear loss.

Evaluation of the Role of Pointing Disorders

To investigate the possible contribution of pointing disorders to the impairment of auditory lateralization, 2 alert and cooperative patients, G.R. and A.B., were requested to adjust the apparatus to the interaural intensity difference yielding

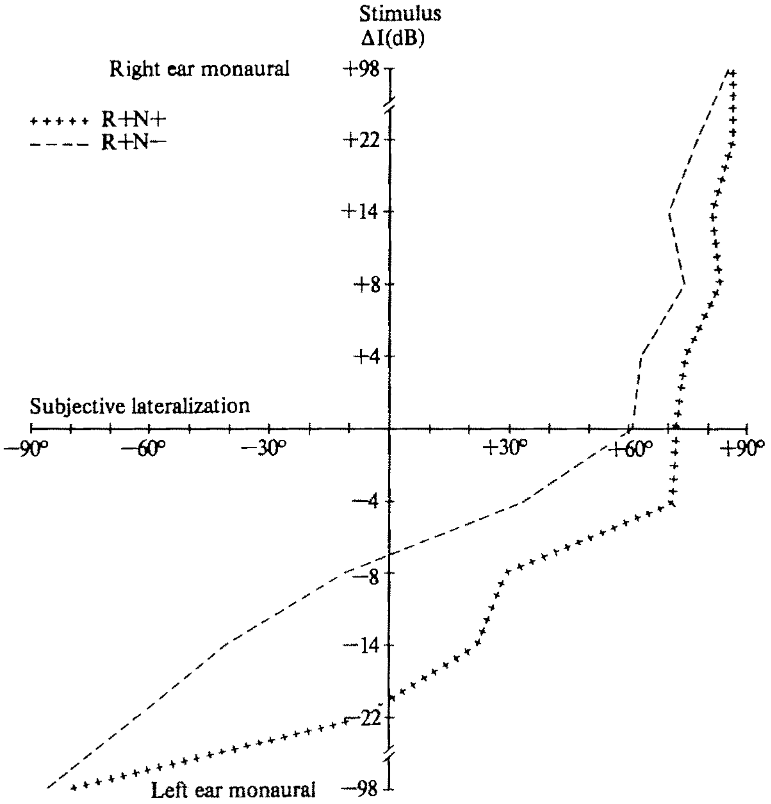

FIG. 2. Lateralization curves in the two subgroups of R+ patients. R+ N+ patients (patients with unilateral neglect), R+ N− patients (patients without unilateral neglect). Ordinate, abscissa and origin of the axes: *see* legend to fig. 1.

a subjective midline localization of the acoustic image, by setting the position of a knob located in front of them in the sagittal midplane. Both G.R. and A.B. did not display interaural differences of hearing loss on pure tone air conduction audiometry. In the starting position of the test the patients received a continuous monaural stimulation; no time limits were imposed for setting the intensity difference. Ten trials randomized in a fixed order were given: in 5 of the trials the starting position was a monaural left ear stimulus, in the other 5 trials *vice versa*. Both G.R. and A.B., in order to yield a subjective midline localization of the acoustic image, gave a more intense stimulation to the left channel: G.R., $\Delta I = -8.80$ dB (SD 9.48); A.B., $\Delta I = -6.40$ dB (SD 7.29). The negative values of the interaural ΔI indicate a more intense stimulus to the left ear. The results appear to be consistent: both patients gave a greater intensity to the left channel in 8 out of 10 trials. These findings do not support an interpretation of the impairment of auditory lateralization in terms of a pointing disorder.

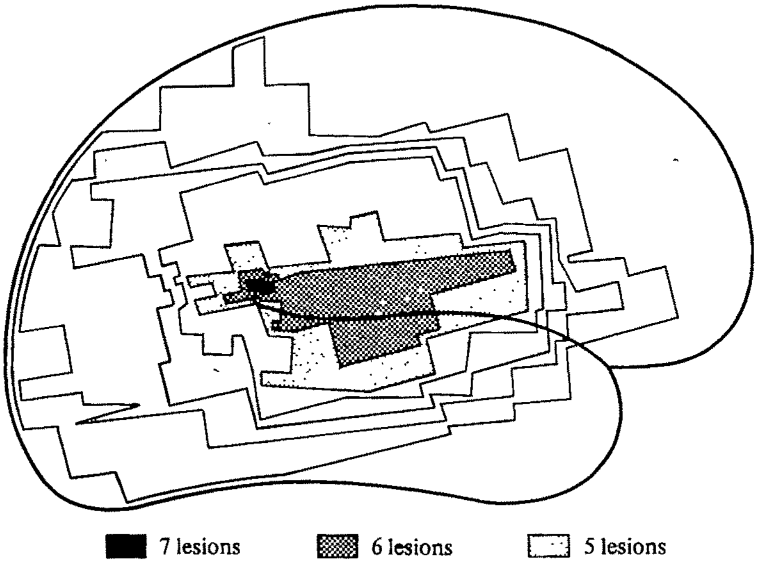

FIG. 3. Composite contour map of the deep and superficial lesions of 10 R+ N+ patients.

Location of Lesion

The location and extent of lesion were assessed in CT scans. Lateral maps of the lesions were reconstructed using the method described by Luzzatti *et al.* (1979). Composite contour maps were then drawn following the procedure described by Howes and Boller (1975). The location of lesion of the patients with defective auditory lateralization was recorded. The R+ patients were subdivided into two groups, according to the presence of neglect. For the sake of comparison, the location of lesion of the L+ patients, who did not display an impairment of directional hearing, was also recorded.

For the R+ N+ patients, 11 cases had a deep and superficial lesion, and 3 cases a deep lesion. In one case the CT scan was negative. Fig. 3 shows the composite contour map of the lesions of 10 patients with deep and superficial lesions. The eleventh patient had an occipito-temporo-parietal deep and superficial lesion, but the CT scan image was not available for mapping. The contours drawn on the standard lateral diagram of the brain represent the degree of overlap of the lesions: the outer line indicates the area affected by one lesion only, the next by two, and so forth. It is apparent that the greatest overlap occurs in the regions surrounding the posterior two-thirds of the sylvian fissure; the supramarginal gyrus appears to be involved in 7 out of 10 cases.

Fig. 4 shows the map for the 3 R+ N+ patients with deep lesions. Examination of the horizontal CT sections showed that Case M.F. had a small deep ischaemic lesion in the white matter of the frontal lobe. In Case F.S. the ischaemic lesion

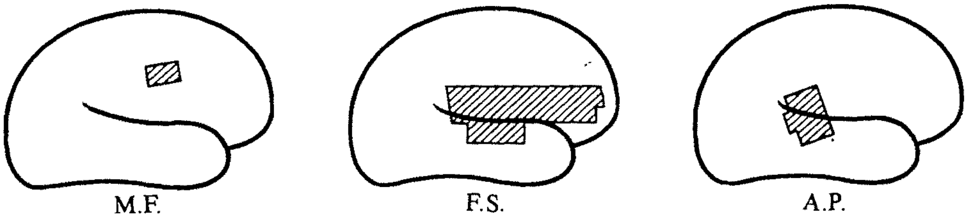

FIG. 4. Lesion maps of 3 R+ N+ patients with deep lesions.

appeared to involve the frontoparietal white matter and the basal ganglia. In Case A.P. there was a haemorrhagic lesion in the thalamus.

Nine out of 10 R+ N− patients had a positive CT scan. In one case no lesion was visible. Fig. 5 shows the composite contour map of the 5 R+ N− patients with deep and superficial lesions. The extent of the damage tends to be smaller than that of the R+ N+ cases. The greatest overlap again involves the regions surrounding the sylvian fissure. However, the inferior parietal lobule seems to be spared, more anterior and more posterior regions being involved.

Fig. 6 shows the composite contour map of the 4 R+ N- patients with deep lesions. Again, the inferior parietal lobule appears to be largely spared. Examination of the horizontal CT sections showed that one case had a lesion in the frontal white matter; in another the frontoparietal white matter was damaged; in 2 cases both the subcortical white matter and parts of the basal ganglia appeared to be damaged.

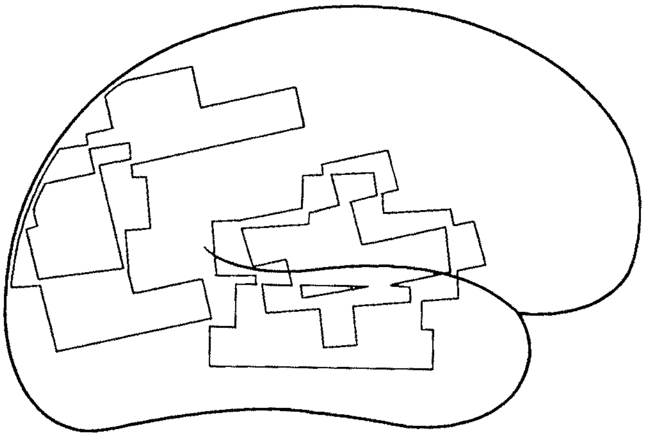

FIG. 5. Composite contour map of the deep and superficial lesions of 5 R+ N− patients. Degrees of overlap: outer line 1 lesion, middle line 2 lesions, inner line 3 lesions.

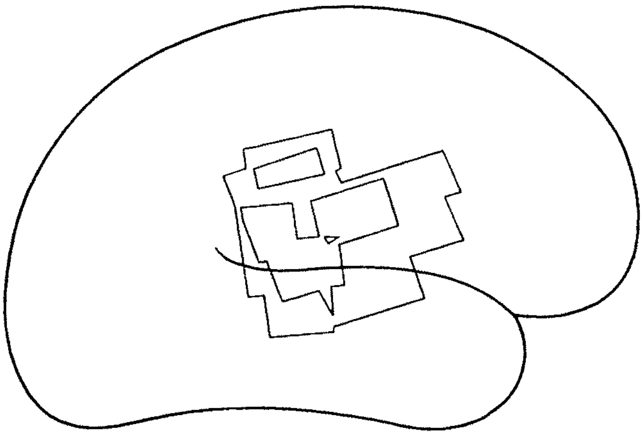

FIG. 6. Composite contour map of the deep lesions of 4 R+ N− patients. Degrees of overlap: outer line 1 lesion, middle line 2 lesions, inner line 3 lesions.

Fig. 7 shows the composite contour map of the lesions of the 9 L+ patients with deep and superficial lesions. In these cases the greatest overlap occurs in the superior temporal gyrus and in the inferior parietal lobule. The tenth patient had a small deep ischaemic lesion involving parts of the basal ganglia. The site and the extent of the lesions of the L+ patients appear comparable to those of the R+ patients. These results seem to rule out the possibility that the present findings may be biased by different locations or extent of the lesions in the two groups of patients with visual field defects.

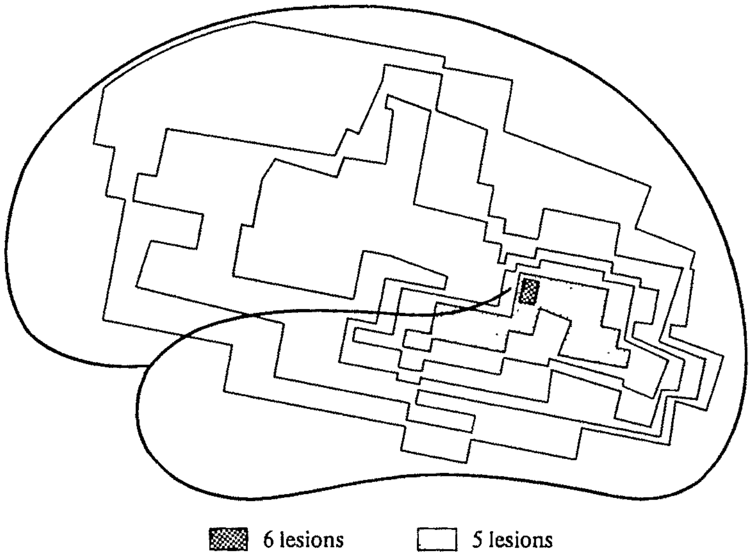

FIG. 7. Composite contour map of the deep and superficial lesions of 9 L+ patients.

DISCUSSION

The reported experiment showed a clearcut hemispheric asymmetry in the disorder of auditory lateralization, namely, that directional hearing is impaired only by lesions involving the right hemisphere.

The present data are not fully consistent with previous findings that, even if lesions of the right hemisphere actually disrupt the ability to localize sounds, damage involving the left hemisphere may impair directional hearing, although less severely (Teuber and Diamond, 1956, quoted by Teuber, 1962; Ruff *et al.*, 1981). Conversely, the observation that only damage to the right hemisphere affects auditory lateralization, producing an SDE towards the ipsilateral side, is in line with the results of Altman *et al.* (1979). These authors, however, who disrupted the hemispheric function by unilateral electroshocks, were not able to investigate the differential effect of anterior *versus* posterior damage of the right hemisphere.

In order to explain the observed pattern of results three hypotheses will be discussed. Two of them, the *selective hearing impairment hypothesis* and the *extinction hypothesis* assume that the processing of the information presented to the left ear is impaired. The *representational hypothesis* does not explain the disorder of lateralization in terms of defective processing of sensory information, but suggests that the internal representation of egocentric space is affected.

According to the *selective hearing impairment hypothesis* only a unilateral lesion of the right hemisphere would cause some defect in the contralateral ear, thus accounting for some of the present results. If such a bias favouring the right ear is assumed in the R+ patients, a rightward SDE is to be predicted, as the interaural ΔI is the effective cue to lateralization. Further, correct lateralization of the left ear monaural stimulus is also predicted because in this condition the right ear does not receive any stimulation. However, a review of the relevant literature does not support this hypothesis either as to the assumption that a unilateral lesion causes a contralateral hearing loss or as to the hemispheric asymmetry of the disorder. The classical position (Jackson, 1876, *see* Jackson, 1931), as well as most subsequent studies (*see* review of Neff *et al.*, 1975), maintains that unilateral lesions do not impair absolute thresholds. Some investigators, however, found a slight impairment of the ear contralateral to the damaged hemisphere. Gersuni (1965) and Karasseva (1972) reported that lesions of the temporal lobe may impair the detection by the contralateral ear of sounds of a few milliseconds in duration, but do not mention hemispheric asymmetries. Karp *et al.* (1969) found a raised threshold of the left ear in 10 out of 19 right brain-damaged patients, but unfortunately their series did not include left brain-damaged patients. On the other hand, the right posterior mislocalizing patients of Ruff *et al.* (1981) had no abnormalities in pure tone thresholds. In our series we did not find any significant contralateral hearing deficit on pure tone audiometry. All these sources of evidence suggest that the hypothesis of a selective contralateral hearing deficit cannot account for the disorder of auditory lateralization of the R+ group.

The *extinction hypothesis* would assume that a unilateral lesion of the right hemisphere impairs perception of the stimulus presented to the contralateral ear, when the ipsilateral ear is simultaneously stimulated; the perception of monaural stimuli is not affected. The mean behaviour of the R+ group is consistent with the extinction hypothesis. An explanation in terms of extinction accounts for the SDE to the right of the R+ patients, as it implies a total or a partial suppression of the left ear stimulus, in conditions of bilateral simultaneous stimulation. However, the behaviour of one individual case of the present series cannot be explained by an extinction mechanism: in M.F. even left ear monaural stimuli are displaced to the right (fig. 8).

Furthermore, the extinction hypothesis provides an explanation of the present findings only if it is assumed that lesions of the left hemisphere are unable to produce auditory extinction. It is usually maintained that damage to either hemisphere can produce extinction, although injury of the minor hemisphere is somehow more frequently associated to this phenomenon (Critchley, 1949). In the auditory modality Bender and Diamond (1965) investigated extinction using simultaneous stimulation with two dissimilar sounds, such as finger snapping and jingling keys, each presented in symmetrical regions of the auditory space, usually near the ears. They found contralateral extinction following lesions of either hemisphere, although the majority of their patients had damage to the right hemisphere. Heilman and Valenstein (1972*a*), using a similar method of stimulation, found a closer association between lesions of the right hemisphere and contralateral extinction. During a ten-month period these authors discovered 17 patients with auditory extinction: in 9 out of 10 cases with a positive brain scan the lesion involved the right hemisphere. However, most dichotic listening studies showed that unilateral lesions of either hemisphere impair perception of the message delivered to the contralateral ear and it has been suggested that extinction accounts for this 'lesion' effect (*see* Goodglass, 1967; Schulhoff and Goodglass, 1969; Sparks *et al.*, 1970).

According to the *representational hypothesis* the disorder of auditory lateralization occurs because the neuronal network which provides the internal representation of egocentric space is disrupted. The selective impairment of right brain-damaged patients implies an asymmetrical distribution of space representation in the two hemispheres. This is in agreement with the hemispheric asymmetries concerning unilateral neglect (*see* the recent review by Mesulam, 1981).

The findings of Altman *et al.* (1979), as well as the results of the present study, show that SDE to the right involves not only the contralateral, but also the ipsilateral half-space. This suggests that not only the contralateral half of the space representation is affected, but that also the ipsilateral half is impaired.

This conclusion is consistent with the results of previous studies of visual localization both in animals and in man. Lamotte and Acuña (1978) observed that in monkeys unilateral posterior parietal lesions impair the reaching for a visual target by the contralateral limb, yielding an SDE towards the ipsilateral side in both half-spaces. In man, the visual localization deficit produced by unilateral lesions is usually confined to the contralateral half-space (*see* Lynch, 1980, and De Renzi, 1982, for reviews). The two available systematic studies, however, show that visual mislocalization can also occur within the ipsilateral half-space. Ratcliff and Davies-Jones (1972) reported that unilateral posterior lesions, which in the majority of cases involved the parietal lobe, can also produce defective localization in the ipsilateral half-space. Inspection of Ratcliff and Davies-Jones's figures suggests that there may be an SDE towards the ipsilateral side. Corin and Bender (1972) showed that visual mislocalization can occur in the ipsilateral half-space with an SDE towards the ipsilateral unaffected side. Although Ratcliff and Davies-Jones did not report hemispheric asymmetries, in Corin and Bender's series 12 out of 19 patients had a lesion of the right hemisphere.

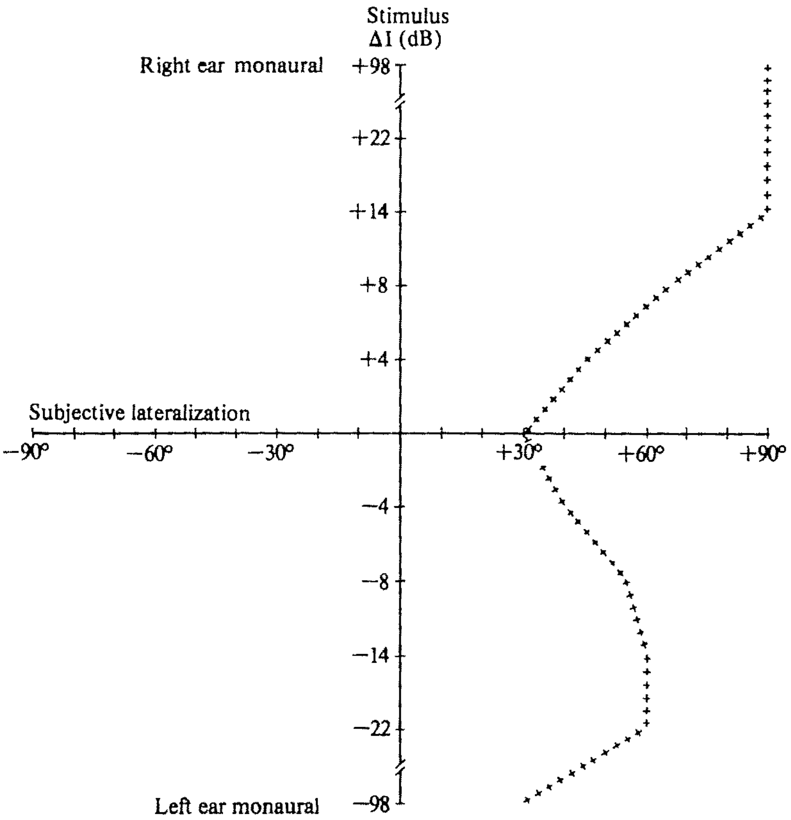

FIG. 8. Lateralization curve of case M.F. (R+ N+). Ordinate, abscissa and origin of the axes: *see* legend to fig. 1.

The behaviour of patient M.F. argues for the representational hypothesis. Nevertheless this constitutes an exception in that all R+ patients except M.F. accurately localized monaural stimuli delivered to the left ear, as predicted by the extinction hypothesis. We observed, however, that several R+ patients showed a tendency to point somewhere to the right and rear towards the neck, although they did eventually localize monaural left ear stimuli accurately. Conversely, they performed with monaural right ear stimuli perfectly and without any hesitation. The representational hypothesis could tentatively account for this behaviour if we consider that for physical reasons it is impossible to point to the right inside the skull.

An important question concerns the relationships between the disorders of auditory lateralization and unilateral neglect. The finding that the defect of auditory lateralization was present in all the R+ patients, independent of the presence of unilateral neglect as assessed by the cancellation task, and that it involved both half-spaces, could be regarded as evidence that different factors underlie the two disorders, as suggested by Ruff *et al.* (1981). However, the patients with neglect showed a greater mean SDE, although their performance did not differ significantly from that of the R+ patients without neglect. It could be the case that the two tasks have a different sensitivity, the auditory lateralization task being a more sensitive tool to detect neglect than the visual cancellation task.

Finally, the site and the extent of the right hemisphere lesions which produce impairment of directional hearing need to be discussed. As to previous studies showing an association between defective auditory localization and right brain damage, Shankweiler (1961) reported that parietal patients make a greater mean error than nonparietal cases. Both Teuber and Diamond (1956) quoted by Teuber (1962) and Ruff *et al.* (1981) showed that posterior lesions yield a greater impairment. In the series of Klingon and Bontecou (1966), the site of the lesion was assessed in 23 of the 31 patients with contralateral mislocalization: in 16 patients the lesion included the parietal lobe and in 4 out of the 7 nonparietal cases the frontal lobe was damaged. To summarize, previous evidence seems to suggest that parietal damage plays a major role.

In the present study some patients had deep lesions involving the thalamus and the frontal lobe. There is evidence that both thalamic (Watson and Heilman, 1979; Cambier *et al.*, 1980; Watson *et al.*, 1981) and frontal lesions (Heilman and Valenstein, 1972*b*) may produce contralateral neglect.

In the vast majority of patients, however, the lesions superimpose on the regions surrounding the posterior two-thirds of the sylvian fissure. When the disorder of auditory lateralization is associated with evidence of contralateral neglect, as assessed by the cancellation task, the lesions tend to be larger than in the cases in which no neglect is shown. The finding that the R+ patients without neglect harbour smaller lesions is consistent with a previous observation (Bisiach *et al.*, 1981). Furthermore, the inferior parietal lobule appears to be damaged when contralateral neglect is present, whereas more anterior regions seem to be involved when no neglect is shown. This dichotomy is consistent with evidence suggesting that lesions comprising the inferior parietal lobule may play a major role in producing contralateral neglect (*see* Mesulam, 1981, for a review). It may be the case that lesions affecting the inferior parietal lobule produce a severe distortion of the inner representation of egocentric space. Conversely, when this region is spared a minor distortion occurs, yielding more subtle disturbances, such as a disorder of auditory lateralization.

ACKNOWLEDGEMENT

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MYORHYTHMIA: A WIDESPREAD MOVEMENT DISORDER

CLINICOPATHOLOGICAL CORRELATIONS

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SUMMARY

The clinical manifestations of 24 cases and the autopsy findings of 6 cases of extremity myorhythmia are presented.

Extremity myorhythmia is that form of myorhythmia in which rhythmic alternating movements predominantly involve the limbs. The main difference between the tremor of extremity myorhythmia and the tremor of parkinsonism is the slower tremor rate, 2 to 3 cycles/s in myorhythmia and 4 to 6 cycles/s in parkinsonism. The mechanograms, except for the slower frequencies in myorhythmia, can be very similar, including sinusoidal oscillation patterns in both conditions.

Myorhythmia may be defined as a coarse, alternating tremor, present at rest and usually during movement, which occurs at rates varying from 50 to 240 oscillations/min but mostly at either 120 to 140 or 160 to 180 cycles/min. The alternating movements may be intermittent or continuous or both types may be present in different body parts. When multiple parts are involved, synchronous or asynchronous movements are about equally common. Movements are usually relatively rhythmic and regular but may vary over periods of time in rate, rhythm or amplitude and rarely so, even over the course of a few hours and are absent during sleep. Movements may involve single limbs, several limbs or a combination of limbs plus face, palate, head, jaw, neck, tongue, eyes or trunk.

The frequency of the movements in the 24 cases varied from 120 to 180 oscillations/min with two exceptions the slowest being 60 and the fastest 240, with most tending to cluster near either 120 or 180 cycles/min.

The most common aetiologies were brainstem vascular disease and cerebellar degeneration secondary to chronic alcoholism-nutritional deficiency. The best prognosis occurred in the latter group.

Clinicopathological correlations in our autopsy series indicate that myorhythmia of the limbs may occur ipsilateral to the dentate nucleus or superior cerebellar peduncle lesions or contralateral to inferior olive involvement. Unilateral lesions of the dentate nucleus may result in bilateral limb movements and bilateral dentate lesions may be associated with unilateral limb movements.

The frequent involvement of the cerebellum and the substantia nigra suggests possible roles for the cerebellum and substantia nigra in the myorhythmia process.

INTRODUCTION

The term myorhythmia was first used to distinguish this form of repetitive adventitious movement from the alternating tremor of parkinsonism (Hertz, 1931). The tremor rate (2 to 4 Hz) was slower than that of parkinsonian tremor, the intervals between single cycles were rather irregular and the frequency and voltage of muscle potentials exceeded those of parkinsonian tremor (Hertz, 1931). According to Hertz, any body part could be involved; however, the head, platysma, facial muscles, pharynx, palate, tongue, larynx and smaller muscles of the limbs were more commonly affected and the abnormal movements often persisted during sleep. Other authors (Guillain and Mollaret, 1932) devised the term 'skeletal myoclonus' in an attempt to differentiate palatal myoclonus from rhythmic involuntary movements not involving the palatal muscles. Later workers also used skeletal myoclonus to refer to rhythmic movements of limb muscles whether or not there was palatal involvement. The terms skeletal myorhythmia or tremor have also been used to describe these movements. Since they have the characteristics of a rhythmic tremor rather than those of clonic jerks it appears to us that myorhythmia is both more accurate and has precedence in the literature.

The slower tremor rate (2 to 3 Hz) differentiates the tremor of extremity myorhythmia from that of parkinsonism (4 to 6 Hz). The mechanograms of both tremors can be very similar, including sinusoidal oscillation patterns.

In one of the early reports of 'skeletal myoclonus', the clinical and pathological aspects of a case involving the left side of the body were presented. The movements were synchronous with palatal myoclonus (Guillain and Thurel, 1932; Guillain *et al.*, 1933). Similar reports were published later (Crouzon and Christophe, 1936; De Savitsch, 1936; Lhermitte and Sigwald, 1941).

Myorhythmia without palatal involvement has been thought to be quite unusual. Clinical reports are rare and there are only a few reports with pathological examinations (Van Bogaert and Bertrand, 1932; Guillain *et al.*, 1934; Garcin *et al.*, 1963).

In this paper we shall consider myorhythmia which involves predominantly the limb muscles (extremity myorhythmia). Over the past ten years we have been able to observe at our hospital 24 cases of myorhythmia without palatal involvement. A number of these patients were followed for many months and during several hospital admissions. In 2 patients (Cases 4 and 6) palatal movements were observed but only two years (Case 4) or three months (Case 6) after extremity myorhythmia had first appeared. The 6 cases with autopsy findings (Cases 2–7) are reported in detail. Clinical data from the other 18 cases are summarized in the Appendix.

MATERIALS AND METHODS

Complete brains of the 6 cases who came to autopsy were available for study. For light microscopic studies haematoxylin and eosin was used as the routine stain. Special stains included phosphotungstic acid-haematoxylin (PTAH) for glial fibres, luxol fast blue for myelin and Bielschowsky silver for myelin and neurons. Paraffin embedding was employed in all cases.

Case Reports

Case 2. An 84-year-old white male was admitted to the hospital in May 1972, six days after the sudden onset of left hemiparesis, dysarthria, dysphagia and urinary incontinence. There was a vague history of a 'slight stroke' with left hemiparesis in 1964. Hypertension had been present since 1965. On admission general physical examination was unremarkable. Significant neurological findings were left hemiparesis, left central facial paresis and left-sided hyperreflexia. Strength in the left leg improved. He was discharged to a nursing home a month later with the diagnosis of branch occlusion of the right middle cerebral artery.

He was readmitted in April 1973, two days after the onset of dysarthria and increased left hemiparesis. On examination, the left hemiparesis and left central facial paresis were much more pronounced than at discharge. EEG showed bilateral anterior slowing with right-sided predominance. Brain scan revealed only slight delay in cerebral perfusion on the right. Following an initial period of improvement, the left-sided weakness became worse on May 23, 1973. Repeat EEG showed worsening of the previous abnormalities; repeat brain scan was unchanged. Pneumoencephalogram on June 1, 1973 showed only moderate dilatation of all ventricles. The patient subsequently developed pneumonia and repeated genitourinary infections. On December 30, 1973 he became lethargic and noncommunicative, but was able to respond to verbal stimuli.

On April 9, 1974 rhythmic movements were observed in the right upper limb, the right corner of the mouth and eyelids. Movements of the right upper limb consisted of rhythmic flexion and extension of the fingers, thumb and wrist at a rate of 136/min, and occurred intermittently in periods lasting several minutes. Lip movements were rhythmic and continuous, also at a rate of 136/min. The eyelids moved bilaterally at the same rate with occasional cessation; they were not synchronous with either the limb or lip movements. There were no tongue, palatal or eye movements. The movements were not precipitated or accentuated by peripheral stimulation; stimulation, in fact, seemed to decrease their intensity. His state of consciousness varied between periods of lethargy and alertness. All movements persisted without change for one month and were present at the time of his transfer to a nursing home on May 5, 1974.

On May 30, 1974 the patient returned to the hospital in acute respiratory distress due to a pneumonic infiltrate and he died on June 6, 1974. There were no spontaneous movements present during this six day interval.

At necropsy, general examination showed laryngitis with mucosal ulcerations and haemorrhages, bilateral hypostatic pneumonia, interstitial pneumonia, pulmonary congestion and focal haemorrhages, severe atherosclerosis of the left anterior descending coronary artery with incomplete occlusion, and bilateral pyelonephritis.

Post-mortem examination of the brain revealed a moderately severe degree of atherosclerosis. The brain weighed 1150 g. The right anterior cerebral artery was occluded by an organizing thrombus. There was massive encephalomalacia in the territory supplied by both the right anterior cerebral artery and the right middle cerebral artery. This involved predominantly the superior, middle and inferior frontal gyri, the superior parietal lobule, insula, basal ganglia, corona radiata and the anterior limb, genu and a portion of the posterior limb of the internal capsule.

The cut surfaces were pale yellowish with a thin orange cortical rim. There were areas of cystic degeneration especially in the region of the insula and basal ganglia. The infarcted area measured 13.5 cm anteroposteriorly, 7.5 cm transversely, and 6.8 cm vertically. The left cerebral hemisphere was grossly unremarkable except for some evidence of oedema and congestion. The right mammillary body appeared to be slightly smaller than the left. The right cerebral crus was smaller than the left. Cut surfaces of the pons and medulla showed atrophy of the right corticospinal and corticopontine tracts and the nuclei pontis and hypertrophy of the inferior olivary nuclei (fig. 1). There was a triangular depressed infarction in the right cerebellar hemisphere measuring 1.3 × 1 × 0.3 cm.

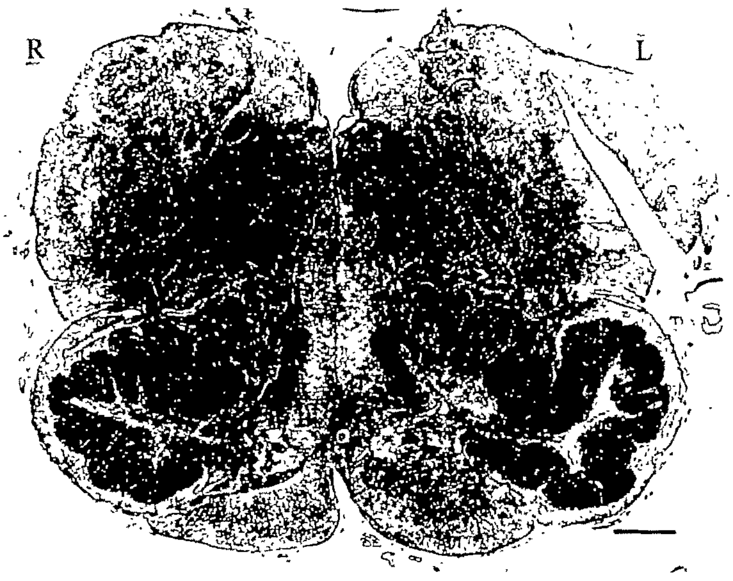

FIG. 1. *Case 2.* Medulla. Bilateral hypertrophy of the inferior olives, greater on the left. The right corticospinal tract is atrophic. (Luxol fast blue-cresyl violet. Bar = 1.5 mm.)

Microscopic study showed infarction with cystic degeneration of the right cerebral hemisphere with secondary degenerative changes involving the right cerebral crus, midbrain, pons and medulla. The left inferior olive (fig. 2) showed spongiosus, degeneration and demyelination of the hilum and hypertrophic degenerated and vacuolated olivary neurons. Less extensive neuronal degeneration was seen in the right inferior olive. Demyelination and gliosis of the hilum were also present in the right inferior olive. The dentate nuclei of the cerebellum and the central tegmental tracts in the midbrain, pons and medulla were normal.

Case 3. A 40-year-old white male was admitted to another hospital in November 1974 in a comatose state after he collapsed while jogging. Extensive investigations, including four vessel cerebral angiography, pneumoencephalography and CT scans, revealed only an occlusion of the right posterior cerebral artery. His neurological state improved to the point where he regained some measure of alertness and he was able to follow simple commands. He remained quadriparetic, unable to speak or swallow, being fed through a nasogastric tube. He developed flexion contractures of the left arm and leg. In January 1975, approximately two months after admission, he developed involuntary movements involving all extremities.

The patient was transferred to the Veterans Administration Hospital, Washington DC on March 13, 1975. Neurologically there was only limited responsiveness to verbal or noxious stimuli. The patient would occasionally look to the left on command. The left pupil was dilated and fixed. The right pupil was small and reacted sluggishly to light. There was limitation of all motion of the left eye except for abduction. There were severe flexion contractures bilaterally with decorticate posturing of the upper limbs. Reflexes could not be elicited due to the contractures. Bilateral Babinski responses were present, together with a marked spastic quadriparesis.

He had slow, rhythmic, resting movements involving the jaw, head, right upper and lower extremities, right pectoral and right thigh muscles. The movements of the jaw, head and extremities were continuous for long periods of time and were present unchanged during most periods of observation over the next six months.

The rhythmic elevation and depression movements of the jaw occurred at a rate of about 150/min and were not synchronous either with the head or limb movements. The head movements consisted of lateral rotation at a rate of 160/min. The right upper limb was maintained in a flexed posture and showed rhythmic abduction-adduction movements of the arm with flexion-extension movements of the right

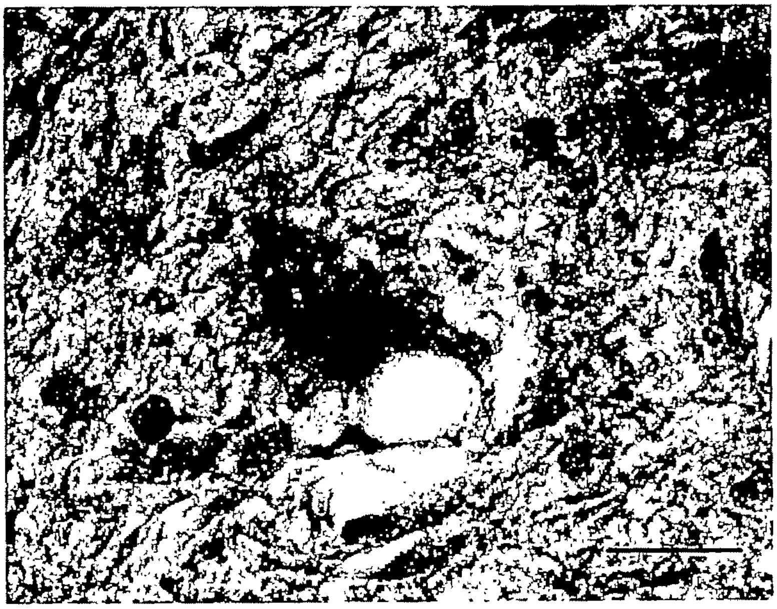

FIG. 2. *Case 2.* Left inferior olive, showing a hypertrophic degenerative and vacuolated neuron. (Luxol fast blue-cresyl violet. Bar = 25 μm.)

hand at a rate of 150/min. Movements of the right leg consisted of adduction-abduction of the thigh at a rate which varied from 140 to 180/min. The arm, leg and head movements were not synchronous. On a number of occasions there were sudden, spontaneous, rhythmic (160/min) contractions in the right pectoral muscle area which persisted for a few minutes and then ceased spontaneously. Similar movements were also seen in the right thigh muscles lasting for about five minutes at a time. The pectoral and thigh movements were not synchronous with the arm and leg. On palpation the amplitude of the thigh muscle contractions was quite variable; on occasion, among the rhythmic contractions there occurred sudden quick movements resembling isolated myoclonic jerks. In addition, at other periods, there were independent, rhythmic contractions of muscles in the anterior surface of the right leg and foot.

There was no evidence of ocular or palatal movements. No movements were observed when the patient was asleep. Peripheral stimulation of any type intensified both the amplitude and the frequency of the movements.

The diagnosis was brainstem infarction secondary to vertebrobasilar artery occlusive disease. The patient was transferred to another hospital on August 15, 1975 where a progressive deterioration was punctuated by several febrile episodes. He died on October 28, 1975.

At necropsy the general examination showed purulent bronchitis and bilateral pneumonia.

The brain weighed 1620 g and showed moderate diffuse cortical atrophy, a normal gyral pattern, no evidence of herniation, and mild to moderate dilatation of the lateral ventricles. Intracranial and extracranial vessels showed virtually no atherosclerotic involvement. There was a large V-shaped infarct involving the ventromedial aspect of the thalamus and hypothalamus bilaterally (fig. 3) and the region of the raphe just ventral to the third ventricle in this region. The lesions were confined to the distribution of branches of the posterior cerebral artery. There were no other gross lesions or areas of encephalomalacia.

Microscopic sections through the hypothalamus, thalamus and the subthalamus revealed old, bilateral softening containing gitter cells. The subthalamic nuclei showed some degree of neuronal loss bilaterally. The substantia nigra showed bilateral neuronal loss, reactive astrogliosis and dispersed melanin granules. The pathological findings seen in the substantia nigra and subthalamic nuclei were considered to be ischaemic in origin. An infarct with gitter cells was seen in the region of the right red nucleus. It extended to the right medial lemniscus and the superior cerebellar peduncles at the point of decussation. The cerebellum including the dentate nuclei was normal. The inferior olivary nuclei were normal.

Case 4. A 39-year-old black male was readmitted to the hospital on July 9, 1974 because of recent difficulty in swallowing. His illness began in 1957 with 'nervousness' and shaking of the head. Over the next few years he had progressive unsteadiness of gait. A diagnosis of olivopontocerebellar degeneration was made during his first admission here on April 30, 1964. The patient's mother also had olivopontocerebellar degeneration confirmed by autopsy.

The neurological examination of the patient in April 1964 revealed truncal ataxia, broad-based gait, markedly impaired tandem walking and a nodding head tremor with lateral rotation. Speech was

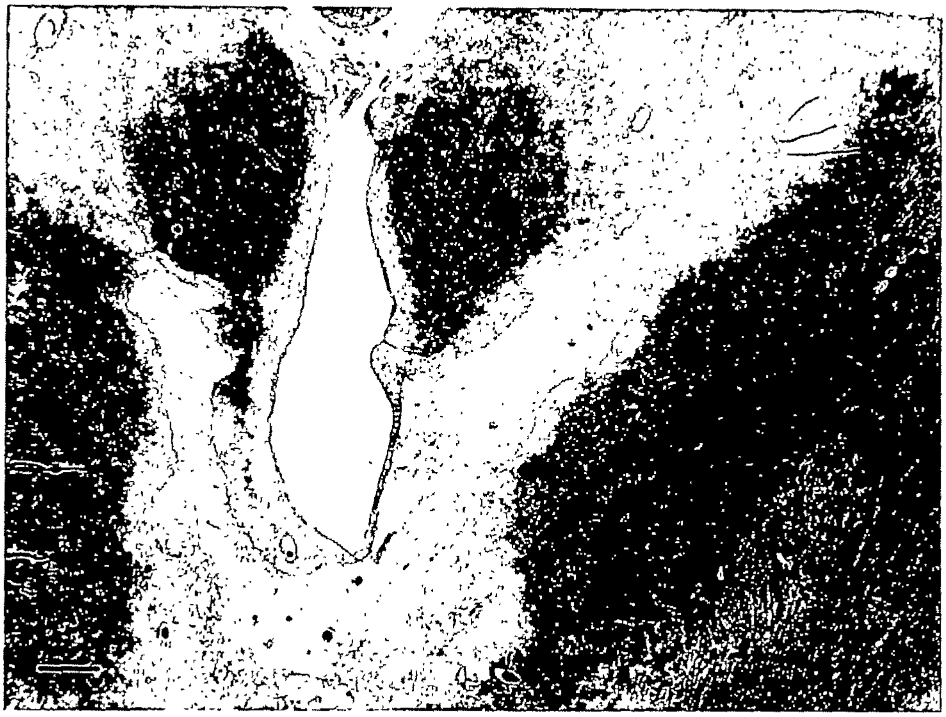

FIG. 3. *Case 3.* Thalamus-hypothalamus. Cavitating infarct involving the ventromedial thalamus and hypothalamus bilaterally. (H and E. Bar = 1 mm.)

markedly dysarthric. Cerebellar functions including rapid alternating movements were impaired in all limbs. Tone, reflexes and sensation were normal and there were no pyramidal tract signs. A pneumoencephalogram was normal without evidence of cerebellar atrophy.

Readmission in 1971 documented further deterioration of cerebellar function without additional abnormalities.

On July 9, 1974 he was readmitted because of difficulty in swallowing. On admission he was alert, orientated and in no acute distress. He showed continuous tremor of the head, mouth, neck and hands. Reflexes were hyperactive bilaterally, but there were no pathological reflexes. There was marked cerebellar dysfunction involving the trunk, head and extremities. He showed large amplitude ataxic movements bilaterally, but there was no intention tremor. There was no evidence of difficulty in swallowing while the patient was in hospital.

Over a period of approximately one month until his discharge on August 9, 1974, the patient was observed to have a variety of slow, rhythmic movements involving the right shoulder, right arm, right hemithorax, right pectoral muscles and right thigh muscles. At times the movements were present only in individual muscles such as the sternocleidomastoid, pectoral or right thigh muscles. At other times, multiple areas and muscles were involved. Movements were intermittent, appeared for four or five minutes at a time, then stopped. The most prominent movements involved the right shoulder, the right upper arm and the right hemithorax.

These rhythmic movements were all synchronous and occurred at a rate of 170 to 180/min. They were characterized by elevation of the shoulder alternating with depression, to-and-fro lateral movements of the chest wall and abduction-adduction movements of the right arm. When the patient was supine, the movements were of lesser amplitude but still present at the same frequency. Peripheral stimulation had no effect on the movements; tension or stress increased both their frequency and amplitude. Limb movements persisted during sustained posture and on finger-to-nose tests. No movements were observed during sleep. There were no palatal movements.

He was readmitted on November 11, 1975 with fever and marked lethargy. There was no change in either the cerebellar manifestations or the myorhythmia. A urinary tract infection secondary to Pseudomonas aeruginosa was treated and the patient's lethargy and fever disappeared. He was discharged to a nursing home on December 1, 1975.

On July 23, 1976 he was admitted from the nursing home because of marked lethargy. Chest x-ray revealed a right middle lobe aspiration pneumonitis. Repeat chest x-rays on August 3 showed a right pleural effusion; this was aspirated with slight clinical improvement. During this period the myorhythmic movements were rarely seen. On August 15 the patient developed a bronchopleural fistula which required chest tube drainage. On the following day a respiratory arrest occurred. He was successfully resuscitated and transferred to the medical intensive care unit. The next day intermittent, resting, rhythmic movements began, involving the head, eyes, trunk, and both arms and legs bilaterally, including the hands, fingers and feet. The movements occurred at a rate of 170 to 180/min. For the first time palatal movements were observed. They were continuous and not synchronous with any of the other movements. The head, eye and limb movements were synchronous. All movements except those involving the palate ceased during sleep. They persisted until he died on September 7, 1976.

Autopsy revealed severe, bilateral necrotizing bronchopneumonia, aspiration pneumonia, bronchopleural fistula of the right lung and right middle lobe abscess.

The brain weighed 1200 g. It showed symmetrical cerebral hemispheres, normal gyral configuration and translucent leptomeninges. The large veins were normal. The extracranial and intracranial vessels showed only scattered foci with slight yellowish intimal thickening and widely patent lumens. There was marked atrophy of the pons and moderate atrophy of the cerebellum and the inferior olives. Sections revealed normal cortical grey matter and central white matter and normal central ganglionic masses. Optic tracts, lateral geniculate bodies and calcarine cortices were normal. Sections of the brainstem and cerebellum showed a wedge-shaped basis pontis with striking atrophy of the ventral part of the pons, atrophy of the superior and middle cerebellar peduncles, inferior olives and the nuclei pontis. The white matter of the cerebellar hemispheres was also atrophic and there was marked atrophy of the dentate nuclei.

Microscopic examination revealed severe atrophy of the olivary nuclei with neuronal loss and gliosis. There was neuronal loss with gliosis and status spongiosus of the basis pontis and a decrease in transverse fibres. In the cerebellum there was loss of Purkinje cells, minimal loss of granule cells, normal molecular layers and marked atrophy of the dentate nuclei with neuronal loss and gliosis (fig. 6). The red nuclei and the central tegmental tracts were normal but the substantia nigra showed diffuse neuronal degeneration, neuronal loss and gliosis.

Case 5. A 60-year-old male with a 33 year history of 'parkinsonism' secondary to traumatic encephalopathy, was admitted to the hospital on June 8, 1976 because of increasing paranoid behaviour. In June 1943 the patient was involved in a truck accident. He was unconscious for fifteen hours and was in hospital for eleven months. While in the hospital in 1944 he experienced difficulty in closing his jaw. Periodically the tongue would protrude involuntarily from his mouth. In 1947 the patient first noticed shaking of his right arm. A number of years later, the shaking extended to the left upper extremity. Between 1949 and 1956 there was progressive diminution in the power of the patient's voice, difficulty in swallowing and mental deterioration. The patient underwent a left stereotaxic thalamotomy in January, 1964. Following this, he developed a generalized seizure and increasing paranoia, the latter considered to be due to a schizophrenic reaction of paranoid type.

He was seen in a follow-up visit on February 12, 1965 at which time the tremor in the right arm was markedly decreased. He had manifested no further paranoid ideas or abnormal behaviour. Neurological examination revealed a 6 Hz tremor in the right arm and a 6 to 7 Hz pill-rolling tremor in the left arm. Tone was mildly increased in the right limbs. The tendon reflexes were normal and there were no pathological reflexes. His tremor was stated later to have returned to preoperative levels.

Following a period of L-DOPA therapy in the latter part of 1970, he was described as showing 75 per cent improvement in limb tremor. In December 1970 L-DOPA was decreased because of choreiform movements. The patient was described as being alert, orientated, cooperative and showing resting tremor of the left arm, face and lower limbs. In May 1976 medication was changed to Sinemet, but this drug had to be discontinued when the patient developed paranoid ideas.

General physical examination on admission on June 8, 1976 was unremarkable. Psychiatric examination revealed visual and auditory hallucinations together with paranoid ideas with no evidence of dementia. Neurologically, he had a flexed posture involving the legs, arms, trunk and head. The facies was masked, he was drooling saliva and spoke in a monotone. There was moderate rigidity of the neck and all four limbs with cog-wheeling of the right arm and leg. The tendon reflexes were decreased and there were no pathological reflexes present. Resting, rhythmic tremors were present in all four limbs. Laboratory studies including CSF, isotope brain scan and CT scan were unremarkable. EEG showed diffuse slowing.

On admission, the rhythmic resting movements involving both upper limbs were characterized by flexion-extension at the elbows and wrists at a rate of 160 to 180/min. Over the next week they became less pronounced and occasionally were seen to involve only the left forearm and hand. At other times a pronation-supination type tremor at a rate of 160 to 180/min was seen in the upper limbs. At still other times movements were present only in the left hand, most pronounced in the left thumb and forefinger with less movement of the other three fingers. These three fingers were held in a flexed position during flexion and extension while the forefinger remained extended at the metacarpophalangeal joint and the thumb made rhythmic opposition movements toward the first phalanx of the third digit. Movements were never synchronous between the upper extremities. Intermittent rhythmic movements of the jaw muscles (masseters) and muscles of the left side of the face at a rate of 160 to 180/min were present most of the time. Periodically there were episodes of synchronous, rhythmic flexion-extension movements of the right arm at the wrist and elbow together with rhythmic contractions of muscles around the left corner of the mouth, lower lip and the infraoral area. These occurred at a rate of 160 to 180/min. None of the movements was ever faster than 180/min and frequently they were well under that rate. There were no movements of the palate and no movements were seen during sleep. During sustained posture and finger-to-nose manoeuvres the left arm movements persisted unchanged while those of the right arm decreased. It was considered that this patient had had a movement disorder of the parkinsonian type up to 1965, but during the final (1976) admission this was myorhythmia.

He showed no improvement on gradually increasing doses of Sinemet. He developed facial dyskinesia and his paranoid ideas increased, so that his medication was discontinued on June 20, 1976. Thereafter, there was no change in either the paranoid manifestations or the myorhythmia. He died suddenly on July 2, 1976.

At autopsy there were multiple pulmonary emboli with occlusion of the main right and left pulmonary arteries and multiple pulmonary infarcts.

The brain weighed 1200 g. The large veins of the brain were normal. The large arteries showed mild yellowish intimal thickening with patent lumens in all vessels. In the anterior portion of the left leaflet of the dura mater there was a hole measuring 1 cm in diameter. Examination of the brain revealed a 1 cm hole in the superior frontal convolution 3 cm from the tip of the left frontal lobe, probably representing the previous operative area. There was mild atrophy of the frontal lobes and thin translucent leptomeninges. Otherwise there was normal cortical grey matter and central white matter and normal thalamic, caudate nuclei, mammillary bodies, hypothalmic nuclei and hippocampi. Optic tracts, lateral geniculate bodies, optic radiations and calcarine cortices were normal. The cerebellum was unremarkable as to folia, central white matter and dentate nuclei. Multiple sections of the mesencephalon, pons and medulla showed markedly decreased pigmentation of the substantia nigra and locus coeruleus. The inferior olives were normal.

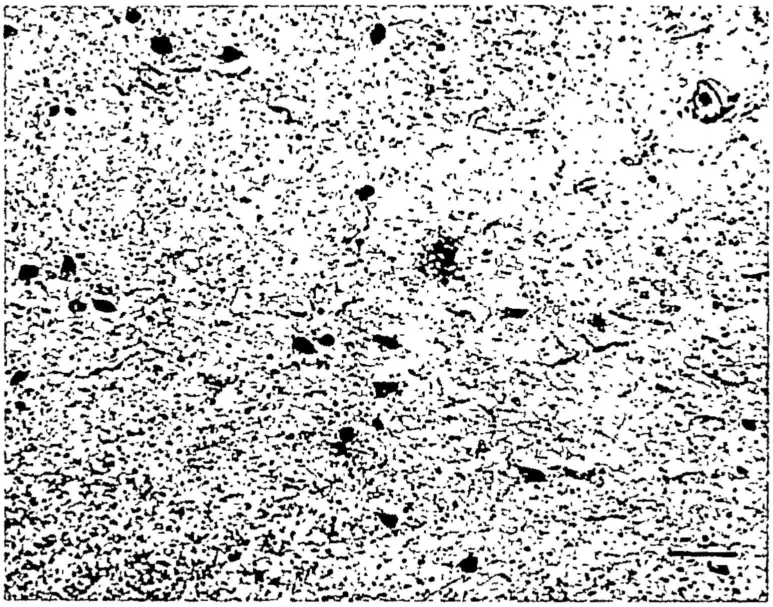

FIG. 4. *Case 5.* Midbrain, showing degeneration and loss of neurons in substantia nigra. (Luxol fast blue-cresyl violet. Bar = 40 μm.)

Microscopic examination showed degeneration and loss of most of the neurons in the substantia nigra (fig. 4). There was astrogliosis and melanin pigment was present in a few macrophages and glial cells. No Lewy bodies were seen. A Bielschowsky silver stain showed neurofibrillary degeneration in the form of thick enlongated, flame-shaped tufts or fine filaments forming coils or compact masses in the cerebral cortex, hippocampi, and oculomotor, facial and vagus nuclei. The dentate nuclei, superior cerebellar peduncles, central tegmental tracts and the inferior olivary nuclei were normal. The findings of degeneration and loss of neurons in the substantia nigra, the absence of Lewy bodies and the presence of neurofibrillary tangles were considered to be consistent with the postencephalitic variety of parkinsonism.

Case 6. A 61-year-old white male, was admitted to the Medical Service of the hospital for the second time on June 30, 1977 with the complaints of generalized weakness, fatigue, shortness of breath and swelling of his legs of one month's duration. The patient's wife stated that in March 1976 he had an episode of right hemiparesis followed several days later by left hemiparesis. This was accompanied by indistinct speech and difficulty in swallowing. These symptoms improved slowly over the next several weeks. However, about one month later intermittent rhythmic movements of all four limbs appeared and persisted to admission.

Physical examination revealed a lethargic individual in moderate distress using accessory muscles of respiration. There were decreased breath sounds and coarse basal rales bilaterally. There was moderate ankle and pretibia oedema. Blood gases indicated metabolic alkalosis and pulmonary insufficiency. Aspiration pneumonia developed and was successfully treated. Blood gases improved following appropriate therapy.

On neurological examination on July 6, 1977 he was alert and orientated but dyspnoeic. Pupils were round, regular, equal and reacted to light and accommodation. He had bilateral internuclear ophthalmoplegia and vertical nystagmus. There was a left central facial weakness. Rapid alternating movements were impaired in the left upper limb and there was bilateral heel-shin ataxia. Sensation was intact. Strength was decreased distally in the arms and proximally in the legs. Reflexes were normal and there were no pathological reflexes.

The most striking findings were intermittent resting rhythmic, asynchronous, flexion-extension movements of all four limbs and the trunk. The limb movements occurred at the rate of 140 to 160/min, disappeared for periods of four or five minutes at a time and then reappeared spontaneously. In addition there were rhythmic, pendular vertical movements of the eyes and rhythmic movements of the palate and larynx. The ocular movements occurred at a rate of 150 to 160/min and were not synchronous with any of the other movements. The ocular, palatal and laryngeal movements were continuous. Palatal movements persisted during sleep. All other movements ceased during sleep. All movements persisted without change until his discharge on July 12, 1977. Diagnoses were old brainstem infarction with myorhythmia, chronic obstructive pulmonary disease and aspiration pneumonia.

He returned to the hospital on July 7, 1978 with complaints associated with his chronic pulmonary obstructive disease. Neurological examination at that time revealed intermittent, rhythmic movements of all four limbs together with palatal movements. The rhythmic, vertical, pendular ocular movements were now intermittent instead of continuous and occurred infrequently. They were of lesser amplitude than one year previously. The extremity movements also occurred less often and were of lower amplitude but unchanged in character and frequency.

On April 6, 1979 he was readmitted to the hospital and treated for aspiration pneumonia. The previously described rhythmic movements persisted with little change. He died suddenly on May 14, 1979.

Autopsy revealed chronic obstructive pulmonary disease, ulcerative oesophagitis, aspiration of stomach contents and pneumonia.

The brain weighed 1325 g. The cerebral hemispheres were asymmetrical with normal gyral configuration and no evidence of herniation. The large arteries in the area of the circle of Willis showed a moderate degree of atherosclerosis. There was an area of cystic encephalomalacia in the right temporo-occipital lobe in the distribution of the right posterior cerebral artery measuring 3.5 cm in anteroposterior diameter, 1.5 cm transversely and 2.5 cm vertically. A cystic lesion was also noted in the left caudate and adjacent white matter at the level of the optic chiasma, measuring 0.4 cm anteroposteriorly, 1 cm transversely and 0.3 cm vertically. Sections through the mesencephalon at the level of the inferior colliculus showed softening and cystic change involving the medial portions of the substantia nigra, the adjacent brachium conjunctivum and portions of the red nucleus. These changes were more marked on the left than on the right. Multiple sections through the cerebellum, pons and medulla showed no gross abnormalities.

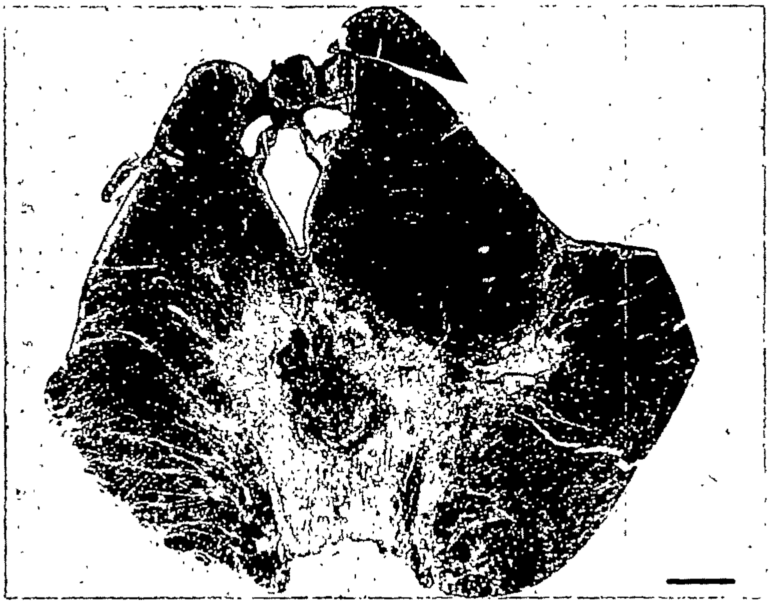

FIG. 5. *Case 6.* Midbrain. Area of destruction involving the midportion of the left substantia nigra, the adjacent cerebral peduncle, the red nucleus and the decussation of the brachium conjunctivum. A smaller lesion involves the right substantia nigra, the adjacent portion of the right red nucleus and the decussation of the brachium conjunctivum. (Luxol fast blue-cresyl violet. Bar = 1.5 mm.)

Microscopically, the area of cerebral encephalomalacia showed both recent and old infarction with cystic changes. Sections of the midbrain showed old encephalomalacia (fig. 5) involving the midportion of the left substantia nigra the adjacent cerebral peduncle, the red nucleus and the decussation of the brachium conjunctivum with degeneration of pigmented neurons and focal collections of histiocytes. A smaller lesion involved the right substantia nigra, the adjacent portion of the right red nucleus and the decussation of the brachium conjunctivum. The cerebellar cortex, dentate nuclei and the inferior olives were normal. The central tegmental tract was probably involved.

Case 7. An 80-year-old black male was admitted to the Medical Service on June 7, 1975 from a nursing home because of dehydration and lethargy. He had a history of long-standing parkinsonism and had been receiving L-DOPA and benzhexol for many years.

On admission he responded only to painful stimuli. Blood pressure was 120/70. Pupils were pin point. The neck and limbs were rigid and there was a fine tremor of the limbs. The tendon reflexes were active and equal, and the plantar responses flexor. CSF studies were normal. Laboratory studies indicated haemoconcentration and uraemia. The EEG was diffusely slow and a brain scan normal. Following treatment of the dehydration, he improved in that he became somewhat more responsive.

On July 2, 1975 the patient was transferred to the Neurology Service. He now appeared to be more alert and was able to state his name on command. He became febrile intermittently and was treated for a urinary tract infection. Between July 11 and July 22, 1975 the patient's state of consciousness varied. There were periods of lethargy and periods when he was able to respond to questions appropriately. A rapid, resting tremor of the limbs was present intermittently. It was less prominent when he was alert and more prominent when he was lethargic.

On July 23, 1975, asynchronous, rhythmic flexion-extension movements involving the upper and lower limbs were observed for the first time. They occurred at a rate of 130/min and were intermittent, lasting for several minutes at a time. He was less responsive than previously. The following day the movements occurred less frequently. He responded by opening his eyes. In the afternoon of July 24, 1975 he had a cardiopulmonary arrest and could not be resuscitated.

Autopsy revealed bilateral bronchopneumonia, healed myocardial infarcts of the anterior and posterior wall of the left ventricle and arteriolonephrosclerosis.

The brain weighed 1100 g. The cerebrum showed cortical atrophy in the frontal and occipital lobes bilaterally with slight narrowing of gyri and widened sulci. The right putamen had an area of softening measuring 0.5 cm anteroposteriorly, 0.5 cm transversely and 1 cm vertically. There was moderate to marked atherosclerosis of the vessels of the circle of Willis. There was greyish-white discolouration of the substantia nigra bilaterally with marked loss of pigmentation in its lateral and medial aspects. The left pons showed a 0.5 cm × 0.5 cm area of softening in the region of the brachium pontis. There was also a 1.0 cm × 0.7 cm × 0.5 cm area of greyish-white softening involving the left dentate nucleus (fig. 6).

Microscopically, there was degeneration and loss of neurons of the substantia nigra especially marked in its lateral and medial portions. Lewy bodies were present in the substantia nigra and the locus coeruleus. The right putamen showed areas of degeneration of neurons and demyelination of adjacent white matter. The left pons in the area of the brachium pontis and the left dentate nucleus of the cerebellum had focal neuronal degeneration, gliosis, demyelination and spongiosus of white matter. The central tegmental tracts, superior cerebellar peduncles and inferior olivary nuclei were normal.

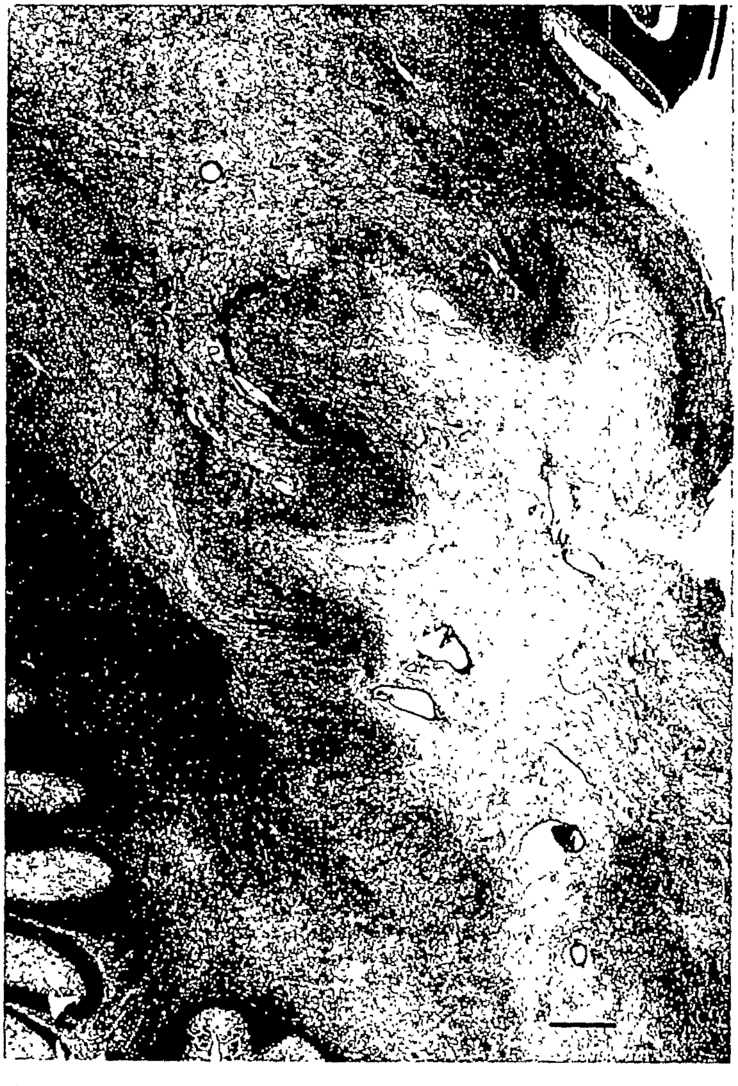

FIG. 6. *Case 7.* Cerebellum. Area of infarction involving the left dentate nucleus. (Luxol fast blue-cresyl violet. Bar = 1.0 mm.)

DISCUSSION

Clinical Manifestations

Multiple periods of observation were necessary to visualize all areas involved in the movement process and to determine the distribution of the movements. The movements in many patients varied from week to week or day to day and at times even over the course of a few hours. The movements would involve single limb, multiple limbs or a combination of limbs plus face, jaw, head or tongue at any one time. Even in those instances where movements of the face, jaw, head, tongue or trunk were present, they always accompanied the limb movements and the limb movements always predominated.

Table 1 summarizes the clinical features of myorhythmia in the 24 cases, including the frequency (rate per minute) of the movement, age at onset, limbs involved, the nature and character of the movement and the aetiology.

The movements were accentuated or suppressed in a few instances by a variety of factors including peripheral stimulation, emotional stress and coughing. In all 24 cases the movements were present at rest and were suppressed by sleep. Sustained posture or voluntary movement accentuated the movements in half of the cases and suppressed them in the remainder.

The 7 patients with cerebellar degeneration and myorhythmia secondary to chronic alcoholism-nutritional deficiency carried the best prognosis in terms of

TABLE 1. MYORHYTHMIA. CLINICAL FEATURES

	No.
Frequency (rate/min)	
60–119	1
120–180	22
181–240	1
Limbs involved	
Single	3
Multiple	21
Synchronous	6
Asynchronous	11
Both	4
Occurrence	
Continuous	5
Intermittent	15
Both	4
Character	
Simple flexion-extension	11
Rotary	4
Complex*	9

	No.
Age at onset (yrs)	
20–29	1
30–39	2
40–49	4
50–59	8
60–69	5
70–79	2
80–89	2
Aetiology	
Brainstem infarct	10
Alcoholic cerebellar degen.	6
MS	2
Hereditary ataxia	2
Viral encephalitis	1
Phenytoin toxicity	1
Collagen-vasc. disease	1
Undetermined	1

* Flexion-extension plus adduction-abduction or supination-pronation.

improvement in the movements. There was complete clearing of movements in 2 of the patients, marked improvement in 1 and notable improvement in the other 4 patients. Both the cerebellar signs and the movements tended to change in parallel suggesting the cerebellum or cerebellar pathways as the site of the involvement. There was no significant improvement in the movements in any of the 10 patients with brainstem infarcts. One patient with multiple sclerosis showed marked improvement but the other patient with more marked clinical signs showed no improvement in the movements. There was progressive worsening of the movements in the 2 patients with inherited cerebellar degenerations and complete clearing in the patient with diphenylhydantoin intoxication.

Analysis of the manifestations of myorhythmia in the 24 cases involving the limbs indicates that this movement disorder is characterized by a 2 to 3 Hz continuous or intermittent, synchronous or asynchronous, relatively rhythmic tremor (most commonly flexion-extension) which occurs at rest and is suppressed by sleep. The myorhythmia usually persists during movement and may be accentuated or suppressed by a variety of factors. It may involve single, multiple or a combination of limbs or limbs plus face, head, jaw, eyes, tongue or trunk and is most commonly due to brainstem vascular disease or cerebellar degeneration secondary to chronic alcoholism-nutritional deficiency. The frequent occurrence of cerebellar manifestations in this series suggests that cerebellar mechanisms play an important role in the pathophysiology of myorhythmia.

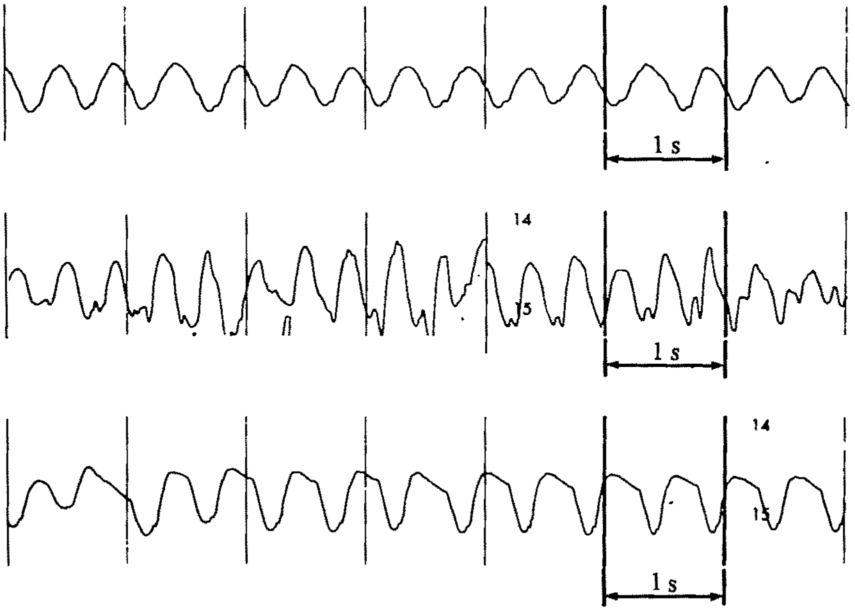

FIG. 7. Mechanogram of a patient with myorhythmia involving the left foot. *Top*, slightly more than 2 Hz myorhythmia. Rest position. *Middle*, increased myorhythmic rate (3 Hz) on voluntary contraction of the left foot dorsiflexors. *Bottom*, no change in the 2 Hz myorhythmia on actively maintained posture of the left leg.

The main difference between the tremor of extremity myorhythmia and the tremor of parkinsonism is the rate, that of myorhythmia being slower, 2 to 3 Hz, as opposed to the 4 to 6 Hz tremor seen in parkinsonism. Both are alternating tremors. Both tremors are present during rest and are suppressed by sleep and may persist or be suppressed during sustained posture or voluntary movement. Accelerometer mechanograms, except for the slower frequencies in myorhythmia, can be very similar in both conditions including sinusoidal oscillation patterns (figs. 7–10).

The slower tremor rate usually provides the clue to the clinical diagnosis of myorhythmia. The important clinical feature, however, is that the tremor is present in the context of a clinical history and neurological findings usually suggestive of brainstem infarction or cerebellar degeneration. The clinical differentiation from parkinsonism is not difficult except in the rare instances where myorhythmia is present in a parkinsonian patient. Ordinarily the tremor of myorhythmia is not accompanied by rigidity, akinesia, postural instability or any of the other manifestations of basal ganglia involvement. The distinctive pill-rolling variety of parkinsonian tremor has not been seen in any of the patients with myorhythmia.

The relationships between extremity and palatal myorhythmia 'palatal myoclonus', and between palatal and ocular myorhythmia 'myoclonus', are still puzzling ones. The frequencies of movement are within the same range. EMG studies of a series of cases of palatal myorhythmia have shown that the frequencies

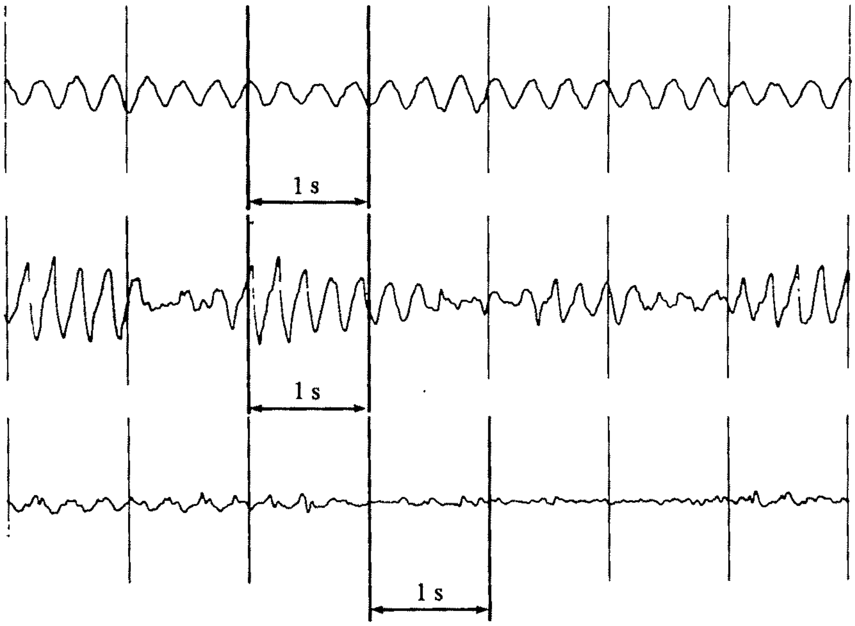

FIG. 8. Mechanogram of a second patient with myorhythmia involving the right hand. *Top*, 3 to 3.5 Hz myorhythmia. Rest position. *Middle*, increased myorhythmic rate (4.5 Hz) on voluntary contraction of the right hand flexors. *Bottom*, suppression of the 3 to 3.5 Hz myorhythmia on actively maintained posture of the right forearm and hand.

varied from day to day and even from moment to moment (Franck *et al.*, 1965) and that frequencies between 150 and 180/min could be associated with myorhythmia of the face at 300 to 600/min and irregular movements of the upper limbs (Rondot *et al.*, 1965). Either palatal or extremity myorhythmia may occur alone or they may on occasion be associated one with the other. When the two conditions occur in the same patient the palatal movement usually persists during sleep while the myorhythmia ceases. Rarely the palatal movements are present during wakefulness and disappear during sleep (Jacobs *et al.*, 1981; Cooper, 1958). In contrast to extremity myorhythmia, palatal myorhythmia is resistant to most peripheral stimulation, emotional stress and posture and can be modified only by voluntary or reflex muscular contraction which may momentarily diminish or stop the myorhythmia (Nathanson, 1956). An EMG study of 4 patients with palatal myorhythmia associated with synchronous ocular myorhythmia showed that during barbiturate-induced drowsiness the palatal movements became irregular in frequency and amplitude and the vertical and horizontal components of the ocular movements became intermittently arrhythmic, asynchronous and markedly diminished in amplitude (Chokroverty and Barron, 1969). One patient has been reported with rhythmic movements of the palate, tongue and jaw associated with synchronous ocular movements in which all movements disappeared during sleep (Cooper, 1958). Three of the 24 cases in our series showed ocular myorhythmia. In

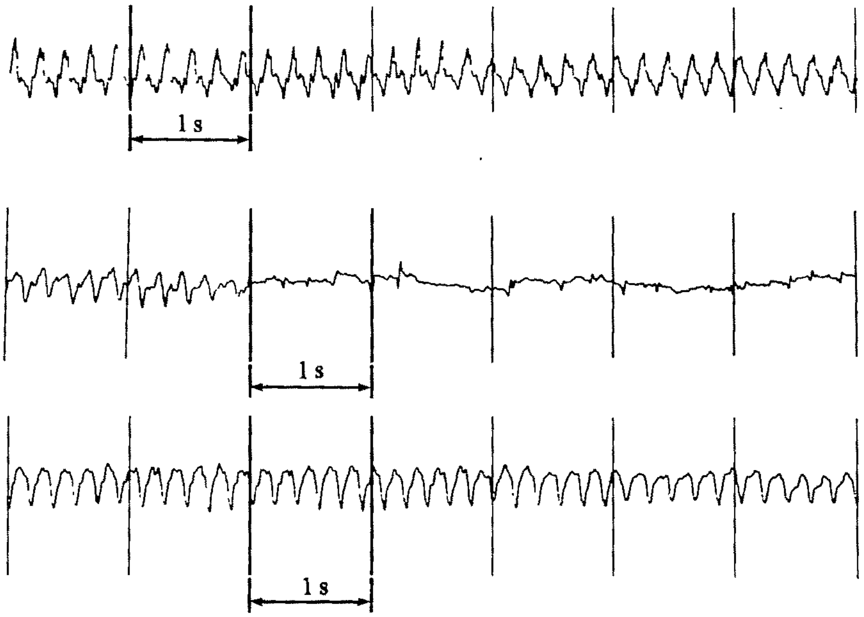

FIG. 9. Mechanogram of a patient with parkinsonian tremor involving the fingers of the left hand. *Top*, 5 Hz rest tremor. *Middle*, suppression of the 5 Hz tremor on voluntary contraction of the left finger flexors. *Bottom*, increased tremor rate (5.5 Hz) on actively maintained posture of the left hand.

all 3 cases the ocular movements disappeared during sleep. Palatal movements present in one of these patients persisted during sleep.

EEG surface electrodes and accelerometers placed over the flexor and extensor muscles or other muscles involved in the myorhythmic movement were used to determine the frequency of the movement. This added little to clinical observation and such counting of the frequency of movement was discontinued.

Pathophysiology

Several theories have been proposed to explain palatal myorhythmia or 'palatal mycolonus'. It has been suggested that it represents the human homologue of a primitive accessory respiratory reflex in gill-breathing vertebrates (Stern, 1949; Yakovlev, 1957). Others have stated that the inferior olive modulates brainstem centres subserving emotional expression and that palatal myorhythmia is a result of release of these centres when the olive degenerates (Herrmann and Brown, 1967). A third idea considers the repetitive palatal movement as a miniature yawning movement (Freeman, 1933). Since palatal and extremity myorhythmia are considered to be forms of alternating tremor, a recent hypothesis explaining the pathophysiology of tremor (Lamarre, 1975) is of interest. In monkeys stereotaxic lesions of the ventromedian tegmentum of the brainstem and the lateral cerebellar system, by removing thalamic afferent impulses, results in a 'Parkinson-like' 3 to 6/s

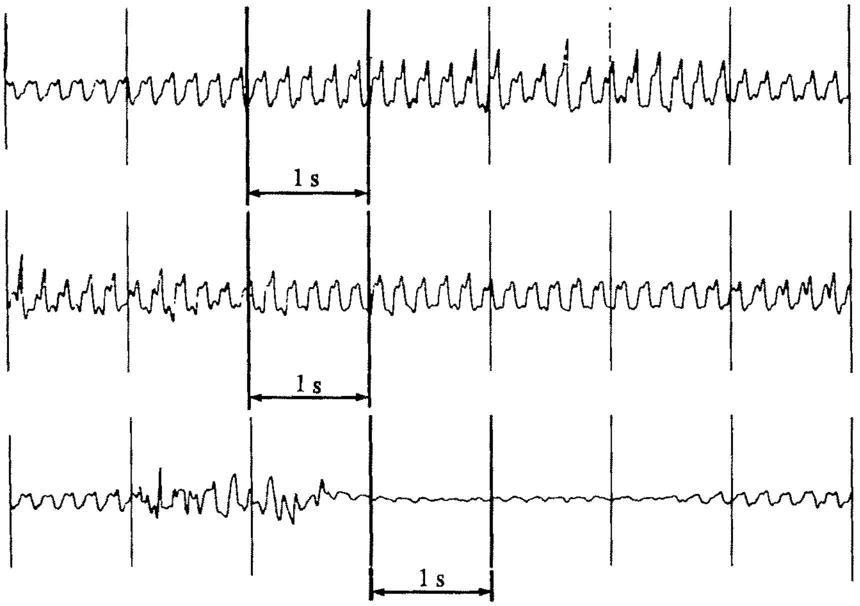

FIG. 10. Mechanogram of a second patient with parkinsonian tremor involving the right hand. *Top*, 5 Hz rest tremor. *Middle*, no change in the 5 Hz tremor on voluntary contraction of the right hand muscles. *Bottom*, suppression of the 5 Hz tremor on actively maintained posture of the right hand.

tremor thought to be thalamic in origin. Harmaline, an MAO inhibitor, injected intravenously in such animals produces a marked increase in the 'Parkinson-like' tremor.

Clinical and Pathological Correlations

Early cases of palatal 'myoclonus' (myorhythmia) who had autopsies showed lesions in the central tegmental tract on one or both sides, and were associated with pseudohypertrophic degeneration of the olivary nucleus (Foix *et al.*, 1926; Gallet, 1927). In other cases the lesions involved the pathway between the inferior olives and the dentate nuclei (Van Bogaert and Bertrand, 1928). Lesions within a classical triangle made up of the ipsilateral dentate nucleus, the contralateral red nucleus and the contralateral inferior olive, in cases of palatal 'myoclonus', were described by Guillain and Mollaret who emphasized the role of the olivodentate complex (Guillain and Mollaret, 1931). However, since the lesions involving the olivodentate fibres within the inferior cerebellar peduncle have been very rare, and in addition have not been associated with palatal myoclonus, this side of Mollaret's triangle has been thought to have no significance. Olivary hypertrophy and palatal myoclonus have frequently been reported with lesions in the ipsilateral central tegmental tract and contralateral superior cerebellar peduncle or dentate nucleus (Davison *et al.*, 1936; Jellinger, 1973). It was felt that the hypertrophy of the olive resulted from transsynaptic degeneration of afferent pathways to the inferior olive through the central tegmental tract (Robin and Alcala, 1975). However, three reports of cases of olivary hypertrophy with lesions in either the central tegmental tract or superior cerebellar peduncle but without palatal myoclonus suggested that tegmental tract and superior cerebellar peduncle lesions result in olivary hypertrophy without palatal myoclonus (Robin and Alcala, 1975). Autopsies of 3 cases of palatal myoclonus reported by Nathanson showed that the primary lesion was in the cerebellum, with the greatest damage involving one of the dentate nuclei (Nathanson, 1956). Retrograde changes were present in the opposite inferior olive indicating that they were the secondary rather than the primary lesions.

In the small number of reports of autopsies on myorhythmia without palatal myoclonus, lesions have been similar to those found in palatal myoclonus except that involvement of the olive has been not only less extensive, but also more atrophic than hypertrophic (Garcin *et al.*, 1963) or even absent (Guillain *et al.*, 1934) and the dentate nucleus has been more severely affected (Van Bogaert and Bertrand, 1932; Guillain *et al.*, 1934; Garcin *et al.*, 1963; Bonduelle, 1968).

In 2 of the 6 autopsies (Cases 4 and 7) in our series the dentate nucleus was involved. Severe atrophy of both dentate nuclei was present in Case 4 and focal degenerative changes and areas of demyelination in the left dentate nucleus in Case 7. The inferior olives were involved in Cases 2 and 4. Case 4 showed atrophy of both inferior olives. Case 2 revealed hypertrophic degenerative neuronal changes with hilar demyelination of the left olive and similar but less pronounced and less widespread changes in the right inferior olive. In only one instance (Case 4) were both the dentate nuclei and the inferior olivary nuclei affected. In Cases 5 and 6 neither the dentate nuclei nor the inferior olivary nuclei were involved. Lesions in the red nucleus were observed in Cases 3 and 6. The central tegmental tract was not affected in 5 of the 6 cases but was probably involved in Case 6. Cerebellar involvement was found in 5 of the 6 autopsied cases. In addition to the dentate nucleus lesions in Cases 4 and 7, the superior cerebellar peduncle was affected in Cases 3 and 6.

TABLE 2. SITES OF PATHOLOGY

	Case No.					
	2	*3*	*4*	*5*	*6*	*7*
Dentate nucleus	−	−	++	−	−	+
Inferior olive	++	−	++	−	−	−
Central tegmental tract	−	−	−	−	−	−
Red nucleus	−	+	−	−	++	−
Superior cerebellar peduncle	−	+	−	−	++	−
Thalamus	+	++	−	−	−	−
Hypothalamus	−	++	−	−	−	−
Subthalamus	−	+	−	−	−	−
Substantia nigra	−	++	++	++	++	++
Cerebellar hemisphere	+	−	++	−	−	−
Brachium pontis	−	−	++	−	−	+

+ = involved. ++ = bilateral involvement. − = uninvolved.

It was of interest and rather surprising that the substantia nigra was involved bilaterally in 5 of the 6 cases (Table 2). This finding would be expected in Cases 5 and 7 because of the parkinsonian manifestations. In Cases 3, 4 and 6, however, parkinsonian manifestations were not present. The substantia nigra is not considered to be part of Mollaret's triangle and palatal myorhythmia due to substantia nigra involvement has not been described previously. Nevertheless, cell loss in the substantia nigra is associated with the tremor and other features of parkinsonism regardless of whether or not there is pathology in other structures. The frequent involvement of the substantia nigra in our cases suggests a possible role for this structure in the myorhythmic process.

The autopsy findings in our series of cases seem to confirm some of the previous experience (Guillain *et al.*, 1934; Garcin *et al.*, 1963). In 1 of the 2 cases with bilateral inferior olive involvement severe atrophy was present and in the other, hypertrophic degeneration. In the case with hypertrophic degeneration of the olive, palatal myorhythmia was not present. The more interesting finding was the absence of olivary involvement in 4 of the 6 cases. Although the dentate nucleus was affected in 2 of the 6 cases, in only 1 was severe atrophy present. In Case 3, in a patient with a sudden brainstem vascular insult who had survived for eleven months, there were lesions in the right red nucleus and the right superior cerebellar peduncle and yet there was no evidence of transsynaptic degeneration of either inferior olive. In Case 6, with bilateral lesions of the superior cerebellar peduncles and the red nuclei, the inferior olives were uninvolved. Uncrossed efferent rubro-olivary fibres from the red nucleus enter the central tegmental tract and project to the principal inferior olivary nucleus. The inferior olivary nucleus also receives fibres from the dentate nucleus suggesting modulation of the inferior olivary nucleus by feedback from the cerebellar nuclei (Carpenter and Sutin, 1983). Lapresle and Hamida (1970) studied serial sections of the dentate nucleus, medulla, mesencephalon and pons in cases of palatal myoclonus with pathological evidence of a complete or partial lesion in the dentate nucleus and evidence of olivary degeneration either grossly apparent or revealed by special staining. It was found that (1) there is a crossed dentato-olivary somatotopy and that small lesions of the dentate nucleus are associated with correspondingly small degenerations of the contralateral inferior olive; (2) there is direct somatotopy between the dentate nucleus and the ipsilateral peduncle; (3) the dentato-olivary pathway, after entering the superior cerebellar peduncle and crossing the midline at its decussation passes the medial and dorsal surface of the red nucleus before becoming part of the central tegmental tract of the contralateral side; (4) lesions near the red nucleus have to involve the dentato-olivary fibres before hypertrophic degeneration occurs in the inferior olive *via* the tegmental tract; and (5) partial lesions of the dentate nucleus were associated with similarly restricted degeneration of the contralateral inferior olive in the complete absence of lesions in the central tegmental tract.

Clinicopathological correlation in our cases reveals some interesting findings. From previous experience in palatal myorhythmia, extremity myorhythmia would be expected contralateral to a lesion of the central tegmental tract and hypertrophied olive or ipsilateral to a lesion in the dentate nucleus or the superior cerebellar peduncle (Robin and Alcala, 1975). In Case 2 the movements affected the right arm and the lesions were present in the inferior olives bilaterally with the left being more affected than the right. The movements were located contralateral to the more involved nucleus. The movements in Case 3 were present in the right arm, right pectoral muscles, right thigh, leg and foot. The lesions in this case were present in the right red nucleus, the right superior cerebellar peduncle, the right thalamus and hypothalamus. The myorhythmic movements were on the expected side since they occurred ipsilateral to the superior cerebellar peduncle lesion. The right side of the body, including the upper limb, shoulder, hemithorax, sternocleidomastoid muscle, pectoral and thigh muscles, was affected in Case 4 by myorhythmic movements. The lesions were located bilaterally and involved both dentate and inferior olivary nuclei. In Case 6, lesions were present in both superior cerebellar peduncles and, as would be expected, bilateral movements were seen. In Case 7 with involvement restricted to the left dentate nucleus, bilateral movements were present. It can be concluded from the correlations between lesions and movements in the present cases that, as in palatal myorhythmia, extremity myorhythmia may occur ipsilateral to dentate nucleus or superior cerebellar peduncle lesions or contralateral to inferior olive involvement. In addition, unilateral lesions of the dentate nucleus may result in bilateral extremity involvement, and bilateral dentate lesions may be associated with unilateral movements of the limbs.

Cases 4 and 5 represented interesting problems in correlations of the lesion with the myorhythmia. The clinical diagnosis in Case 4 was olivopontocerebellar degeneration. Right-sided myorhythmic movements involved the right arm, right shoulder, hemithorax, right sternocleidomastoid, pectoral and thigh muscles. The pathological findings consisted of atrophy of the inferior olives, cerebellar atrophy with severe atrophy of the dentate nuclei, severe demyelination of central cerebellar white matter and Purkinje cell involvement. Myorhythmic movements are rarely seen in inherited degenerative cerebellar disease despite the fact that involvement of the dentate nuclei is common (Bonduelle, 1968). The variability of clinical and pathological findings in different families with these disorders probably accounts for varying opinions concerning the pathological findings. There is disagreement as to whether or not the dentate nuclei and their efferent fibres are involved in olivopontocerebellar degeneration (Escourolle and Poirier, 1973; Brown, 1976; Blackwood and Corsellis, 1976). It has been suggested by Konigsmark and Weiner (1970) that olivopontocerebellar atrophy can be divided into 6 main types. Type 1, the Menzel variety, appears to be closest to Case 4 in clinical and neuropathological findings. Eight families of this variety were described in which there were at least 4 cases with severe neuronal loss in the dentate nuclei and no myorhythmic movements. On the other hand, Bruce (1940) reported 'rhythmic tremor of the limbs' in 5 cases of olivopontocerebellar degeneration.

Case 5 was one of long-standing parkinsonism probably postencephalitic in origin. It was felt that the patient had both parkinsonian tremor and myorhythmia. At times movements were present only in the left hand and were pronounced in the thumb and forefinger. The thumb made rhythmic opposition movements towards the first phalanx of the third finger. This movement had the characteristics not of a pill-rolling tremor but of a midbrain tremor (Denny-Brown, 1968). The major pathological involvement in this case was restricted to the substantia nigra which showed almost complete degeneration and loss of neurons, and the absence of Lewy bodies. Other findings consisted of neurofibrillary tangles in the cerebral cortex and brainstem nuclei, focal perivascular haemorrhages and perivascular haemosiderin-laden histiocytes in the basal ganglia and hippocampus.

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APPENDIX

MYORHYTHMIA. DETAILS OF 18 CASES

Case	*Age at onset (yrs)*	*Duration*	*Distribution and characteristics of myorhythmia*	*Rate/min*	*Additional neurological manifestations*	*Clinical diagnosis*
1	50	2½ y	Progressive involvement of L. cheek, L. upper and lower limbs, R. leg, head, neck, tongue, R. arm and eyes. Continuous, usually synchronous extremity movement. Accentuated by painful peripheral stimulation, coughing and eye opening.	136–140	Bilat. ophthalmoplegia, L. ptosis, bilat pyramidal tract signs with weakness 4 limbs.	High brainstem infarction.
8	25	3 y	Intermittent upper limb (most prominent on the L.), upper eyelids and jaw, synchronous interspersed with asynchronous contractions. Extremity movements markedly intensified by voluntary movement. Also intensified by sustention posture.	140–160	Bedridden spastic paraplegic; marked weakness and incoordination of upper limbs; paresis of conjugate gaze; scanning speech; bilat. Babinski responses; pin prick, touch and position deficits in the limbs.	Multiple sclerosis.
9	40	8 m	Continuous flexion-extension movement, R. elbow with synchronous contractions of R. face and R. neck muscles; less frequent asynchronous similar movement in the L. upper limb, movements in R. upper limb ceased for about 2 min when R. forearm was extended voluntarily.	60	Lethargic, mentally slowed, confused at times; optic neuropathy, R eye; hard shiny exudates both fundi; moderate generalized weakness and wasting of all 4 limbs, most pronounced R. arm.	Chronic encephalopathy, aetiology undetermined, probable collagen-vascular disease.

Case	*Age at onset (yrs)*	*Duration*	*Distribution and characteristics of myorhythmia*	*Rate/min*	*Additional neurological manifestations*	*Clinical diagnosis*
10	31	2 w	Continuous R. leg, R. and L. hands; intermittent in ant. neck muscles and larynx; movements in scattered muscles throughout body; runs of myoclonic jerks either localized or producing movement at joints.	120	Ataxic gait, intention tremor and dysmetria in arms; diminished pin prick and position sense in legs, Marcus Gunn pupil, R. eye, visual acuity 20/60. R. corrected with pin hole and 20/50 L., fields severely constricted.	Multiple sclerosis.
11	50	8 d	Intermittent all 4 limbs, circumoral muscles, L. frontalis, eyelids, eyes (rhythmic horizontal with jerk component), rhythmic rocking of hips and pelvis, generalized myoclonic jerks; myoclonic twitching localized to R. side palate without vertical movement of palate usually seen in palatal myoclonus.	180	Lethargic, anarthric; inability abduct R. eye, L. pupil larger than R., bilat. horizontal and vertical nystagmus, absent gag reflexes and inability to swallow, R. hyperreflexia with R. Babinski, L. spastic hemiparesis	Brainstem infarction.
12	75	1 m	Intermittent adduction-abduction movements of R arm; stopped suddenly when patient yawned or coughed.	120	Lethargic, L. hemiparesis, increased tone legs, bilat. Babinski responses, L. homonymous hemianopia, complete L. ptosis, almost total bilat. ophthalmoplegia. L. central facial palsy, decreased corneal reflexes, miotic pupils with poor response to light.	Brainstem infarction.
13	51	2 w	Continuous R. arm, intermittent other limbs, movement visible in only one at a time; improvement over 2 w period, less frequent and less intense on discharge.	120–180	Wide-based gait, impaired tandem walking; marked ataxia R. arm and both legs, moderate ataxia L. arm, diminished reflexes, decreased pin prick; position and vibratory sensation in feet.	Diffuse cerebellar degeneration, myorhythmia secondary to chronic alcoholism-nutritional deficiency.
14	40	4 y	Asynchronous intermittent, all 4 limbs and head including adduction-abduction of thighs and rocking movements of pelvis, frequently precipitated or accentuated by touch or other stimuli. Gradual improvement over 4 w period.	140–160	Scanning cerebellar speech, truncal ataxia with head and trunk titubation; diffuse weakness and wasting all 4 limbs with impaired rapid alternating movements and limb ataxia, intention tremor arms, absent ankle jerks, distal vibratory deficit legs.	Cerebellar degen., peripheral neuropathy, chronic alcoholism, myorhythmia secondary to chronic alcoholism-nutritional deficiency.
15	46	7 m	Intermittent, legs, arms and pelvis, usually asynchronous, occasionally synchronous, increased in frequency and intensity during periods of emotional stress, or actively maintained posture; unaffected by voluntary movement or peripheral stimulation; gradual decrease in arm movements—infrequent at discharge, pelvic movements ceased completely. Improvement seemed to parallel improvement in cerebellar manifestations.	120	Disorientated in time and place, impaired recent memory, horizontal and vertical nystagmus; marked weakness legs; trunk and ataxia 4 limbs; reflexes diminished legs; touch, pin prick and position decreased legs.	Peripheral neuropathy, encephalopathy, cerebellar degen., myorhythmia secondary to chronic alcoholism-nutritional deficiency.
16	60	9 m	Continuous, synchronous L. shoulder, L. forearm, jaw and L. foot; no change in character or frequency over 9 m period.	120–180	Conscious, responded to verbal commands by closing eyes and opening mouth, moved eyes on command or following, no other voluntary movement, bilat. exotropia, no eyeball movement above or medial to midline, paralysed R. and L. arms, L. Babinski.	High brainstem infarction.
17	52	3 w	Intermittent, legs, present in both supine and sitting positions; ceased completely several days before discharge; seemed to parallel marked improvement in cerebellar manifestations.	140–160	Marked gait ataxia and ataxia 4 limbs, plantar flexor responses; good strength; stocking sensory deficit to pin; touch and vibration, decreased reflexes in legs.	Cerebellar degen., peripheral neuropathy, myorhythmia secondary to chronic alcoholism-nutritional deficiency.
18	60	4 w	Intermittent R. arm and leg, independent similar movements R. foot, movements disappeared during final week in hospital; only mild improvement in gait and mental state.	120–140	Marked thoracolumbar scoliosis to L., trunk and gait ataxia, ataxia 4 limbs with intention tremor arms, impaired memory, judgement and abstract thinking; atrophy R. forearm, R. triceps and L. quadriceps, R. shoulder fasciculations, proximal weakness thighs, absent L. knee and ankle jerks; hyperactive R. knee jerk; bilat. Babinski responses; distal stocking-glove sensory deficit to pin and touch.	Inherited cerebellar disease, peripheral neuropathy, myorhythmia secondary to chronic alcoholism-nutritional deficiency.

Case	*Age at onset (yrs)*	*Duration*	*Distribution and characteristics of myorhythmia*	*Rate/min*	*Additional neurological manifestations*	*Clinical diagnosis*
19	50	9 m	Intermittent, upper and lower limbs and tongue; decrease in frequency and amplitude of movement but still present at discharge, some improvement in mental state and gait.	160–240	Impaired orientation; poor recent memory; wide-based gait; impaired rapid alternating movements and coordination in 4 limbs, decreased achilles reflexes, moderate diffuse weakness, sensory deficit to pin and position legs.	Chronic encephalopathy, cerebellar degen., peripheral neuropathy, myochythmia secondary to chronic alcoholism-nutritional deficiency.
20	56	2 y	Intermittent, both arms, R. wrist and pelvis, persisted in supine position, head and trunk movements not observed in supine position.	140–180	Wide-based unsteady gait; markedly impaired tandem gait; ataxia 4 limbs with intention tremor in arms, impaired rapid alternating movements; head and truncal titubation; extraocular movements impaired on upward and lateral gaze, positive Bell's phenomenon; increased reflexes; flexor plantar responses; intact mentation.	Diffuse cerebellar degeneration, aetiology undetermined.
21	53	1 m	Intermittent, R. leg and intermittent synchronous flexion-extension thigh movements, the latter persisted when patient placed in supine position. Some improvement, less frequent movements prior to discharge.	120–140	Mild diffuse arm weakness, moderate bilateral psoas and hamstring weakness; reflexes decreased in legs, stocking-glove sensory deficit all modalities; impaired coordination in arms; unsteady gait with titubation of trunk; bilat. ataxia legs.	Cerebellar degen., peripheral neuropathy, myorhythmia, all secondary to chronic alcoholism-nutritional deficiency.
22	65	3 m	Intermittent, arms, 1 w after admission developed R. hemiparesis, which improved; the myorhythmic movements more frequent and more intense after this and still present at discharge.	120–180	Alert, disorientaated; markedly impaired recent and remote memory and impaired judgement; broad-based ataxic gait; mild R. hemiparesis; intention tremor and postural tremor in arms with ataxia 4 limbs, increased reflexes R. arm, bilat. Babinski responses; R. ptosis; bilat. horizontal nystagmus.	Peripheral neuropathy, dementia, cerebellar degen., secondary to chronic alcoholism, brainstem infarction. with myorhythmia.
23	76	6 w	Intermittent L. arm, L. shoulder, L. lower face, pendular vertical eye movements.	120–140	R. flaccid hemiparesis, R. Babinski, 1 m after admission ocular myoclonus, vertical downbeat nystagmus, palatal myoclonus, bilat. Babinski responses, anarthria, reacted to painful stimuli, unable to follow commands.	L. hemisphere infarction, brainstem infarction.
24	53	4 w	Initially continuous R. foot and intermittent L. foot, later intermittent R. and L. feet.	120–180	Truncal ataxia, bilat. horizontal and vertical nystagmus, impaired rapid alternating movements, bilat. ataxia 4 limbs, inability to walk unassisted, dystonic movements and posturing both arms, lethargy.	Phenytoin intoxication.

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MOOD DISORDERS IN STROKE PATIENTS

IMPORTANCE OF LOCATION OF LESION

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SUMMARY

In a selected group of right-handed patients with single stroke lesions of either the right (n = 14) or left (n = 22) hemisphere and no predisposing factors for psychiatric disorder, we found that the severity of depression was significantly increased in patients with left anterior lesions as opposed to any other lesion location. In addition, the severity of depression correlated significantly with proximity of the lesion on CT scan to the frontal pole in the left anterior group. The right hemisphere lesion group showed the reverse trend: patients with right posterior lesions were more depressed than patients with right anterior lesions, who were unduly cheerful and apathetic. These findings suggest that intrahemispheric lesion location is in some way related to mood disorder in stroke patients and that there is a graded effect of lesion location on severity of mood change. The neuroanatomy of the biogenic amine-containing pathways in the cerebral cortex might explain this graded effect and provide a neurochemical basis for the mood change.

INTRODUCTION

During the past several years we have been investigating the occurrence of mood disorders following cerebral ischaemia (Robinson and Szetela, 1981; Robinson and Benson, 1981; Robinson and Price, 1982; Lipsey *et al.*, 1983; Robinson *et al.*, 1983*a*). We have reported that the frequency and severity of these mood disorders are significantly increased during the period from six months to two years poststroke, and that, in the majority of cases, they last eight to nine months untreated (Robinson and Price, 1982). In addition, we have found that the course and severity of depressive disorders depend on which hemisphere is injured (Robinson and Price, 1982; Robinson *et al.*, 1983*a*) and, in two studies, one involving left hemisphere injured patients (Robinson and Szetela, 1981) and one involving patients with bilateral brain injury (Lipsey *et al.*, 1983), we reported that the severity of depression was significantly correlated with the proximity of the left hemisphere lesion to the frontal pole as measured on CT scan.

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Previous investigators have reported that left hemisphere brain injury is associated with depressive mood while right hemisphere brain injury is associated with apathy, cheerfulness, and a tendency to minimize difficulties (Gainotti, 1972; for review, *see* Pearlson and Robinson, 1982). It has also previously been reported that the intrahemispheric location of the lesion is important in determining the psychopathological manifestations of brain injury (Andersen and Havnik, 1950; Benson, 1973). In general, left frontal injury has been associated with depressive symptoms while left parietal injury has been associated with unconcern and unawareness (Benson, 1973). In the right hemisphere, Ross and Rush (1981) have described a loss of ability to express emotion with more anterior lesions and a loss of emotional recognition with more posterior lesions, analogous to the language organization in the left hemisphere.

However, the importance of the frontal lobe and the strong relationship between distance of the lesion from the frontal pole on CT scan and severity of depression have not been reported by other investigators. Our original observations in patients with left hemisphere injury were undertaken in a group of patients who were many months past the onset of their illness and in whom there was marked variability in the duration of their illness (Robinson and Szetela, 1981: Robinson and Benson, 1981). In addition, we did not exclude any patients in whom there were premorbid risk factors for psychiatric disorder such as alcoholism, family or personal history of psychiatric disorder. Therefore, in the current study, we examined a selected group of acute stroke patients within a few weeks of their injury who had identifiable lesions on CT scan and no risk factors for psychiatric disorder. There were two aims of this study. The first was to see if we would replicate our previous findings in a better controlled study of patients with left hemisphere injury, and secondly to see what would be the relationship between lesion location and psychopathology in patients with right hemisphere lesions.

METHODS

Patient Population

Over a two-year period, we have screened a consecutive series of 184 patients admitted to the University of Maryland Hospital with either a thromboembolic stroke (n = 144) or intracerebral haemorrhage (n = 40). Of this number, 53 patients could not be interviewed because of a decreased level of consciousness or severe aphasia with comprehension deficits, 7 patients were discharged before they could be examined, and 1 patient refused the interview. Of the 123 patients who were examined, we excluded subjects for the present study if they were left handed, or had a previous personal history of psychiatric treatment, alcohol or drug abuse, family history of psychiatric disorder or if there was a clinical history or CT scan evidence of previous brain injury or the present stroke was not localized on CT scan to one hemisphere. A total of 48 patients survived these exclusion criteria. Of these 48 patients, only patients with lesions which were visualized on CT scan were included. Twenty-two patients met the criteria and had a positive CT scan with a single left hemisphere lesion (6 had intracerebral haemorrhage), while 14 met the criteria and had a single right hemisphere infarct (2 had intracerebral haemorrhage). The fact that in 25 per cent of the patients the lesion was not visualized on CT scan is not unusual since the lesion may have been too small and the tissue changes necessary to produce the needed density contrasts on CT scan were still evolving during the first few weeks after an infarct (Valk, 1980).

Psychiatric and Neurological Examination

The neurological examination and diagnosis were made by the attending neurologist (T.R.P.) in accord with the examination and diagnostic criteria used by the multicentre NINCDS Pilot Stroke Data Bank (Kunitz *et al.*, 1979).

After obtaining informed consent, patients were given a series of standardized quantifiable measures of mood, intellectual function and physical impairment which we have previously found to be reliable and valid in stroke patients (Robinson and Szetela, 1981; Robinson and Benson, 1981; Robinson *et al.*, 1983*b*). Examinations were administered in private between 11 a.m. and 2 p.m. in order to minimize any possible effect of diurnal mood variation. The Hamilton Depression Scale (Hamilton, 1960), a 17 item questionnaire measuring psychological and physiological symptoms of depression, was filled out by the interviewer. The Zung Depression Scale (Zung, 1965), a 20 question self-rated depression questionnaire was read to each patient, and their responses were scored using the four Zung categories. The modified Present State Examination (PSE) (Wing *et al.*, 1974), a semistructured psychiatric interview which elicited symptoms related primarily to mood and anxiety, was examiner-scored. The reliability and validity of this modified version of the PSE has been demonstrated in a previous publication (Robinson *et al.*, 1983*b*). The Mini-Mental State Examination (Folstein *et al.*, 1975) is an 11 item questionnaire which has been found to be reliable and valid in assessing cognitive function in stroke patients. Scores may range from 0 to 30, and a score of 23 or below is indicative of significant cognitive impairment. The Johns Hopkins Functioning Inventory (Robinson and Szetela, 1981) is a 10 item questionnaire which evaluates the patient's degree of independence in activities of daily living such as walking, dressing and eating. Scores may range from 0 to 27.

Analysis of CT Scan

All CT scans were performed on the same scanner using identical slice thickness, angle to orbital-meatal line and size reduction. Analyses of CT scans were done on 9 consecutive dorsal slices 10 mm apart beginning with the first slice that included frontal lobe tissue.

Overall brain size, excluding ventricles, and lesion size were determined in each CT slice by a computerized area calculation procedure. The area within the lesion was divided by the area within the brain, excluding the ventricles, giving the lesion size as a percentage of brain volume. Lesion borders on each slice were determined along the anterior-posterior (AP) axis, and a mean anterior and posterior border as a percentage of the maximum AP distance was calculated. The criterion used for establishing whether a lesion was anterior or posterior was as follows. The lesion was anterior if the anterior border of the lesion was rostral to 40 per cent of the AP distance and the posterior border was anterior to 60 per cent of the AP distance. On the other hand, a lesion was posterior if its anterior border was posterior to 40 per cent of the AP distance and the posterior border was caudal to 60 per cent of the AP distance. Thus, we allowed a 20 per cent overlap of anterior and posterior lesions. Lesions that were anterior to 40 per cent of the AP distance and posterior to 60 per cent were not used in the data analysis and were called both anterior and posterior.

Statistical Analysis

Statistical analysis was done using means and standard deviations, analysis of variance, student's t-tests, and Pearson correlation coefficients. Nonparametric statistics were done using χ^2 tests with Yates modification for small number cells. In order to allow a single depression score to be correlated with other variables, an overall depression score (range 0 to 15) was calculated based on the three depression measures, (i.e. Zung, Hamilton, and PSE) as described in a previous publication (Robinson and Szetela, 1981). Briefly, the Zung, Hamilton and PSE scores were each translated to a five-point scale, and the scores were summed for each patient. A Zung score of < 40 = 0, 40–49 = 1, 50–59 = 2, etc.; Hamilton < 5 = 0, 6–7 = 1, 8–9 = 2, etc.; PSE < 7 = 0, 8–9 = 1, 10–11 = 2, etc. We have translated each depression measure to a five-point scale in order not to 'overweight' one scale, and they can be summed because of high interscale correlation (*see* Results) and previously described cross validation (Robinson and Szetela, 1981; Robinson *et al.*, 1983*b*).

RESULTS

Patients

Background information revealed no statistically significant differences between the right and left hemisphere lesion groups (Table 1). There were 10 patients with left anterior lesions, 8 with left posterior lesions (4 patients could not be classified into anterior or posterior), 6 with right anterior lesions and 6 with right posterior lesions (2 could not be classified), and there were no statistically significant intergroup differences in background demographic data for these four lesion location groups. The patients were predominantly black males in their late fifties or early sixties from the middle or lower socioeconomic class. Patients were interviewed generally within the first two weeks after the stroke.

Neurological Findings

Except for aphasia, there were no significant differences in the neurological symptoms of the left and right hemisphere stroke groups (Table 2). Between 72 and 90 per cent of the patients had a hemiparesis. Between 33 and 67 per cent of both groups had a hemisensory loss, and about 20 per cent had a homonymous hemianopia. Aphasia was found only in patients with left hemisphere lesions, although 2 patients with right hemisphere lesions had slurring of speech. Approximately 28 per cent of the left hemisphere damaged patients were aphasic with an

TABLE 1. CHARACTERISTICS OF STUDY POPULATION

	Location of stroke lesion	
	Left hemisphere (n = 22)	*Right hemisphere* (n = 14)
Age (mean ± SD)	57 ± 12	61 ± 10
Sex (% male)	53	73
Race (% black)	67	63
Socioeconomic class (Hollingshead cl. 4 or 5)	40	45
Marital status (% married)	90	82
No. children (mean ± SD)	1.6 ± 1.3	2.5 ± 2.1
Origin (% rural)	33	54
No. siblings (mean ± SD)	4.5 ± 3.9	4.8 ± 4.0
Tobacco use (% 1 pack per day or greater)	57	46
Previous medical illness (%) (life threatening)	10	27
Time since stroke (mean days ± SD)	12 ± 11	10 ± 7

approximately equal distribution of Broca's, Wernicke's, global and anomic aphasias. Comparison of anterior-posterior groups on each side showed 10 of 10 patients with left anterior infarct had a hemiparesis while only 3 of 8 patients with a left posterior infarct had this symptom $\chi^2 = 4.5$, ($P < 0.05$); 5 of 6 patients with right anterior lesions were hemiparetic while 4 of 6 with right posterior strokes had this symptom (n.s.). There were no other statistically significant differences in neurological symptoms between the anterior and posterior groups.

There were 6 of 22 patients with left hemisphere lesions and 2 of 14 with right hemisphere lesions who had intracerebral haemorrhages. Of these 6 with left hemisphere haemorrhages, 2 had anterior and 3 had posterior lesions (1 was both anterior and posterior) while in the right hemisphere, none had an anterior haemorrhage and one had a posterior haemorrhage (1 was both anterior and posterior). This distribution of infarcts and haemorrhages by location is not significantly different than a random distribution ($\chi^2 = 2.9$, $P > 0.25$).

Relationship of Anterior-Posterior and Right-Left Lesion Location to Psychopathology

Although about half of all patients with lesions of either the right or left hemisphere demonstrated symptoms of anxiety and worrying, there were distinct symptom clusters which were found more frequently in one group than another. Depression and vegetative symptoms (i.e. early morning awakening, decreased appetite and weight loss or decreased libido) were found in 14 of 22 patients with left hemisphere injury and in only 2 of 14 patients with right hemisphere injury ($\chi^2 = 9.4$, $P < 0.01$). When the intrahemispheric lesion location was taken into

TABLE 2. NEUROLOGICAL DEFICITS

	Lesion location			
	Left hemisphere		*Right hemisphere*	
	Anterior	*Posterior*	*Anterior*	*Posterior*
Weakness				
Mild	5/10	2/8	3/6	0/6
Severe	5/10	1/8	2/6	4/6
Sensory deficit				
Mild	3/10	2/8	1/6	1/6
Severe	0/10	2/8	0/6	1/6
Homonymous hemianopia	1/10	2/8	1/6	1/6
Visual neglect			0/6	2/6
Aphasia			—	—
Broca	1			
Wernicke		2		
Global	1	1		
Anomic		1		

account 7 of 10 patients with left anterior lesions had depression and vegetative symptoms while 3 of 8 patients with left posterior lesions, 0 of 6 with right anterior lesions and 1 of 6 with right posterior lesions had these symptoms ($\chi^2 = 8.22$, df = 3, $P < 0.05$). On the other hand, patients with right hemisphere lesions were found to have inappropriate cheerfulness in 6 out of 14 cases (5 of 6 cases were in right anterior group) while this symptom was found in none of the 22 patients with left hemisphere injury ($\chi^2 = 8.6$, $P < 0.01$).

Analysis of scores from the depression scales were also consistent with the finding of right-left hemisphere group differences as well as anterior posterior group differences. Patients with left anterior hemisphere infarcts had significantly higher mean depression scores than patients with left posterior lesions or right anterior lesions on all three depression scales (Table 3). The right posterior group differed from the left anterior group on the PSE and the overall depression score (Table 3).

TABLE 3. INTRAHEMISPHERIC LESION LOCATION RELATED TO DEPRESSION, IMPAIRMENT, SEVERITY, AND SIZE OF LESION

	Left hemisphere		*Right hemisphere*	
	Anterior	*Posterior*	*Anterior*	*Posterior*
	n = 10	n = 8	n = 6	n = 6
Depression scores (mean ± SD)				
Zung	51 ± 12	36 ± 7*	35 ± 7*	42 ± 12
Hamilton	10 ± 6	4 ± 6*	5 ± 2*	7 ± 6
PSE	18 ± 11	5 ± 3*	5 ± 6*	8 ± 6+
Overall	8.4 ± 5.3	2.6 ± 3.4*	1.5 ± 1.2*	5.0 ± 3.5**
Cognitive impairment				
Mini-Mental	19 ± 7	20 ± 6	27 ± 2+	23 ± 5
Activities of daily living				
JHFI	10 ± 6	5 ± 4	5 ± 6	8 ± 5
Lesion volume as % of brain volume	4.7 ± 3.5	6.3 ± 6.1	4.1 ± 4.9	5.0 ± 3.4

* Significantly different from left anterior, $P < 0.01$ + $P < 0.05$. ** Significantly different from right anterior, $P < 0.02$. PSE = Present State.

In contrast to the findings in the left hemisphere, patients with right anterior lesions had significantly lower mean depression scores on the overall depression score than patients with right posterior infarcts (Table 3).

As another way of examining this issue of whether the psychopathological symptoms vary with lesion location, we assessed diagnostic symptom clusters related to site of lesion. Using psychiatric Research Diagnostic Criteria (Spitzer *et al.*, 1975), 6 of 10 patients with left anterior infarcts met the criteria for a diagnosis of major depressive disorder with the exception that in some patients, the duration of symptoms at the time of evaluation was less than two weeks and they, of course, all had brain injury (Table 4). Only 1 patient with a left posterior lesion met the symptom criteria for the diagnosis of major depression while 3 of 8 patients with posterior lesions and 1 of 10 with an anterior lesion, met the symptom criteria for a minor or dysthymic depression, although, again, the duration of symptoms criteria was not met. This distribution of diagnostic symptom cluster by left hemisphere lesion location was statistically different than a random distribution ($\chi^2 = 4.4$, $P < 0.05$).

TABLE 4. INTRAHEMISPHERIC LESION LOCATION AND PSYCHIATRIC DIAGNOSIS

	Left hemisphere		*Right hemisphere*	
	Anterior (10)	*Posterior (8)*	*Anterior (6)*	*Posterior (6)*
Major depression	6	1	0	1
Minor depression	1	3	0	1
Hypomania (PSE)	0	0	5	1
None	3	4	1	3

Among the patients with right hemisphere strokes, 1 patient with a right posterior lesion had the symptoms of major depressive disorder and 1 patient had the symptoms of minor depressive disorder while no patients with right anterior lesions were depressed. Five of 6 patients with right anterior lesions were unduly cheerful (termed hypomania on the PSE), while only 1 patient with a right posterior lesion had this symptom ($\chi^2 = 5.3$, $P < 0.02$) (Table 4). These patients with inappropriate cheerfulness did not meet the diagnostic criteria for any specific psychiatric disorder.

Relationship of Specific CT Scan Measurements to Psychopathology

Within the group of left anterior lesion patients, their depression score correlated with the distance of the lesion from the frontal pole ($r = -0.92$) (fig.). When both the left anterior and left posterior lesion patients were included, the correlation fell to $r = -0.54$ ($P < 0.05$). This was because some of the patients with posterior lesions had significant depression (i.e. 1 with major depression and 3 with minor depressive symptoms), although the overall correlation coefficient continued to be statistically significant and show the same basic phenomenon—that is, the closer the lesion was to the frontal pole, the more severe the depression.

Lesion volume was 4.7 ± 1.1 SE per cent of total brain volume for the left anterior hemisphere group and correlated with the severity of depression ($r = 0.72$). There were no significant differences in the mean lesion volumes between the anterior and posterior groups (Table 3). Lesion volume did not correlate significantly with depression in the posterior group nor the combined anterior and posterior group.

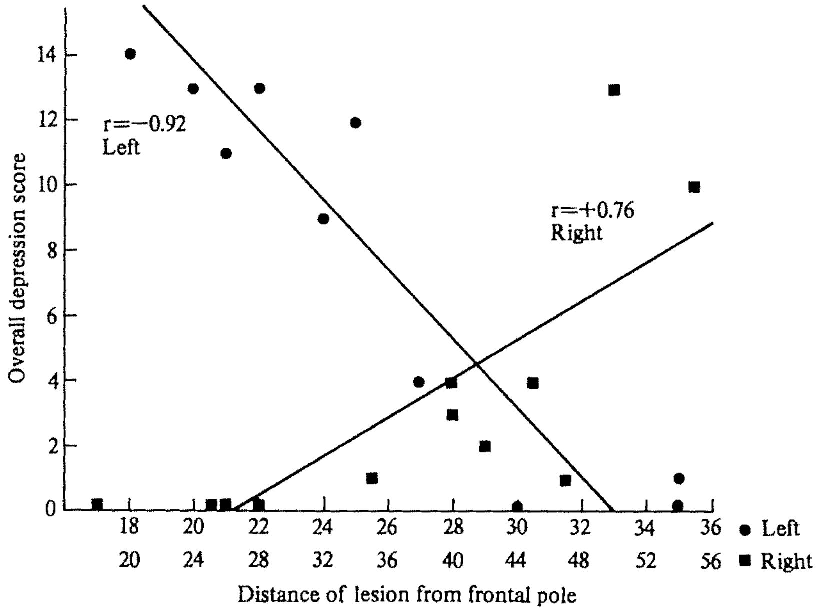

FIG. Relationship between overall depression score and distance of the anterior border of the lesion from the frontal pole for patients with either left anterior hemisphere infarcts or right hemisphere infarcts. The distance from the frontal pole is expressed as a percentage of the total anteroposterior distance. The correlation coefficients are indicated on the figure. r_{left}, $P < 0.001$; r_{right}, $P < 0.01$.

In the group of patients with right hemisphere strokes, there was a significant correlation between the overall depression score and the distance of the lesion from the frontal pole for the entire right hemisphere group (r = 0.76) (fig.), that is, the further the lesion was from the frontal pole, the more severe the depression. This is exactly the opposite direction of correlation from that found in the left hemisphere group. Lesion volume was 4.5 ± 1.3 SE per cent of total brain volume. The lesion volume did not correlate significantly with the depression score in either the anterior or posterior group.

Relationship Between Depression Scores and Physical and Cognitive Impairment

Cognitive impairment as measured by Mini-Mental score, correlated significantly with the overall depression score in the left hemisphere lesion group (r = −0.43); however, activities of daily living as measured by the Johns Hopkins Functioning Inventory (JHFI) score did not correlate significantly with the overall depression score (r = 0.29). In addition, Mini-Mental score, but not JHFI score, correlated with lesion volume (r = −0.63, $P < 0.01$) for the entire left hemisphere lesion group. No other correlations between severity of impairment and depression scores or lesion volume were significant in the left hemisphere injured group.

In the right hemisphere lesion group neither the Mini-Mental score nor the JHFI score correlated significantly with the depression scores. The Mini-Mental score, but not the JHFI score, correlated significantly with the lesion volume ($r = -0.42$, $P < 0.05$). The three depression measures were highly significantly correlated with each other (Zung-Hamilton, $r = 0.80$; Zung-PSE, $r = 0.82$; Hamilton-PSE, $r = 0.85$).

Relationship Between Aphasia and Psychopathology

Although the neurological deficits found in the patients with right and left cerebral stroke were comparable, aphasia was found, as would be expected, only among patients with left cerebral injury. In order to evaluate whether aphasia was an important factor in the predominance of depression in left hemisphere stroke patients, we compared left hemisphere lesion patients with and without aphasia on the various psychopathology scales. There were no significant differences in the mean Zung, Hamilton or PSE scores between patients with aphasia and patients without aphasia. In a previous publication, we have noted the high frequency of depression in patients with nonfluent aphasia (Robinson and Benson, 1981). In the present study, aphasia was found in 2 patients with left anterior lesions, 1 of whom had the symptoms of a major depression and 1 of whom had the symptoms of minor depression. Because there were only 2 patients with aphasia, it was not possible to determine whether the frequency of depression was higher among these patients as compared with patients with left anterior brain injury and no aphasia. However, of the 7 patients who had the symptoms of major depression, only 2 had aphasia (1 with Broca's and 1 with posterior lesion and global aphasia).

DISCUSSION

We have demonstrated in a selected group of patients with single brain lesions and no predisposing factors for psychiatric disorder that there are important and statistically significant differences in the distribution, frequency and/or severity of depression between patients with anterior or posterior lesions within each hemisphere. In addition, we have shown that severity of depression correlates with distance of lesion from the frontal pole across the entire right hemisphere and across the entire left hemisphere although the correlation is strongest within the left anterior group.

This finding in the left hemisphere lesion group is a confirmation of our previously reported findings in a group of chronic brain-injured patients (Robinson and Szetela, 1981) and in patients with bilateral brain injury (Lipsey *et al.*, 1983). It should be noted, however, that the anterior and posterior groups had some overlap in their lesion locations and that the distribution of lesion locations did not cover the entire hemisphere. As shown in the fig. the most anterior lesion was no closer to the frontal pole than 18 per cent of the A-P distance. Thus, we were evaluating lesions which were distributed over about the middle two-thirds of the hemisphere and were only 'relatively' more anterior or posterior. Another point which should be made is that in the right hemisphere group we showed a correlation between severity of depression and distance of the lesion from the frontal pole. Since the patients with right hemisphere injury as a group had less severe depression than left hemisphere lesion patients, the range of scores was lower and the correlation was heavily dependent on two patients with moderate to severe depression. In addition, the interesting finding of inappropriate cheerfulness in patients with right anterior strokes could not be correlated with distance of lesion from the frontal pole because we were unable to 'grade' inappropriate cheerfulness and could, on the PSE, only note its presence or absence. It is possible that severity of this symptom might correlate with proximity of the lesion to the frontal pole as depression did in the left hemisphere lesion group.

The most obvious implication of this study is that the aetiology of the mood disorders found in these stroke patients is in some way related to the location of their brain injury with left anterior injury being particularly associated with depression and right anterior injury associated with inappropriate cheerfulness. The major question, however, is the nature of this relationship. Does the depression represent a psychological reaction to a particular cognitive or physical impairment or does it represent the behavioural manifestation of neurophysiological and neurochemical responses to brain injury? We cannot fully answer this question at the present time and it is possible, for example, that severity of visuospatial deficits in right posterior lesion patients might correlate strongly with severity of depression. In addition, we have recently reported in our longitudinal study of 103 stroke patients that both severity of cognitive impairment and severity of impairment in activities of daily living correlate significantly (r values between 0.3 and 0.4) with depression (Robinson *et al.*, 1983*b*). We are also in the process of a more detailed analysis of neuropsychological impairment using a much more extensive test battery to examine the specific kinds of deficits which may correlate with severity of depression. Thus, it seems highly likely that severity of impairment plays a role in at least some poststroke depression, the issue is only whether there is evidence for additional factors contributing to these mood disorders.

There are several lines of evidence which suggest that neural factors may be involved. First, this interesting relationship between the proximity of the lesion to the frontal pole and severity of depression is a phenomenon which we have repeatedly demonstrated in several studies (Robinson and Szetela, 1981; Lipsey *et al.*, 1983). This 'graded' effect of lesion location on severity of depression is different from the topographical (Broca, 1861; Wernicke, 1908; Penfield and Boldrey, 1937; Geschwind, 1970) or mass action (Lashley, 1963) relationships between any neuropsychological function and lesion location. Secondly, the strength of the correlation between distance from frontal pole and severity of depression explains 50 to 70 per cent of the variance while the relationship to physical or overall cognitive impairment explains 10 to 20 per cent of the variance. Thirdly, the characteristic syndrome-like nature of the depression in many of the patients with left anterior lesions, including both mood and vegetative changes, suggests an 'endogenous' aetiology for the depression. Finally, we have yet to find a specific impairment which occurs in all or most of the severely depressed patients. For instance, Broca's aphasia was found in only 1 of the 6 patients with left anterior lesions and major depressive symptoms. Another patient with an anterior lesion and global aphasia did not have major depressive symptoms and 5 of 7 patients with major depressive symptoms did not have aphasia.

If some of these poststroke depressions do not represent an understandable reaction to impairment, how then might these findings be explained? The most obvious explanation is that we have found a 'frontal syndrome' that is different in the two hemispheres (i.e. left lesions associated with a depressive syndrome, right lesions associated with inappropriate cheerfulness). Numerous investigators have described a 'frontal syndrome' and recognized the importance of the frontal lobes in affect (Hécaen and Albert, 1975). However, there is no known neuroanatomy or neurophysiology to account for the importance of the frontal lobe in affect. Our present findings have not only shown a frontal syndrome, but have also shown a graded effect of lesion location on mood from anterior to posterior. These two findings (i.e. the importance of the frontal lobe in mood disorders and the graded effect of lesion location on mood) suggest an intriguing neural hypothesis for these results.

Numerous investigators have described the arborizing innervation of the cerebral cortex by noradrenergic neurons in rats (Ungerstedt, 1971; Pickel *et al.*, 1974) and in monkeys (Foote *et al.*, 1981) and Morrison *et al.* (1979) have recently demonstrated that lesions of the anterior cortex disrupt these noradrenergic fibres to a significantly greater extent than do posterior lesions. Our laboratory experiments have demonstrated that focal cortical lesions in rats produce widespread but asymmetrical depletion of catecholamine concentrations depending upon which hemisphere is injured (Robinson, 1979; Robinson and Coyle, 1980; Pearlson and Robinson, 1981). Therefore, perhaps the 'lateralized frontal affective syndrome' might be a behavioural manifestation of asymmetrical depletion in the cortical biogenic amine pathways with more anterior lesions producing greater depletion of these amines. Since we were unable to correlate the degree of inappropriate cheerfulness in patients with right hemisphere lesions and proximity of lesion to the frontal pole, we do not know whether this hypothesis is also applicable to the right hemisphere lesion group. It should be noted, however, that our finding of increased depression with more posterior lesions runs counter to what would be expected on this hypothesis.

Although this suggestion is strictly a hypothesis, there are several strengths to proposing such a hypothesis at this early stage of investigation. First, it is a testable hypothesis which makes certain predictions. For instance, a large lesion should interrupt more pathways than a small lesion in the same location, and therefore lead to greater depression. Our finding of a positive correlation between size of lesion and severity of depression in the left anterior group is consistent with this prediction. In addition, it would be expected that concentrations of biogenic amines which have been implicated in the aetiology of functional depressions (Bunney and Davis, 1965; Schildkraut, 1965) would be decreased in the spinal fluid of patients with depression, and we are currently evaluating this prediction by measuring catecholamine metabolites in the CSF of depressed stroke patients. This hypothesis also has the advantage of taking an old observation that there is a distinct 'frontal affect' and giving it an underlying neuroanatomical substrate.

Regardless of what may be the aetiology of these poststroke mood disorders, this study suggests that there may be an important relationship between both inter- and intrahemisphere lesion location and mood disorder and that depressive disorders are both common (i.e. 13 of 30 patients had clinically significant depression) and frequently severe. We need to obtain further data on the aetiology of these disorders as well as to investigate effective treatment techniques.

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LEFT HEMISPHERE INVOLVEMENT IN LEFT SPATIAL NEGLECT FROM RIGHT-SIDED LESIONS

A COMMISSUROTOMY STUDY

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SUMMARY

Current views of the unilateral neglect syndrome caused by right-sided focal lesions generally imply that the left hemisphere is lacking in awareness for the left half of the body and surrounding space. Questioning this assumption on the basis of previous split-brain and hemispherectomy observations, we applied lateralized tests for left hemineglect in three subjects with complete forebrain commissurotomy. Results for the left disconnected hemisphere revealed substantial awareness for the left side of the body and also for extrapersonal space, far greater than suggested by the unilateral lesion data. It is inferred that the left hemisphere, functioning independently, possesses the requisite cognitive mechanisms needed to prevent the appearance of the typical neglect syndrome as observed following right-sided lesions. It is proposed that the eventual explanation of this disorder must therefore account for the lack of left hemisphere compensation.

INTRODUCTION

The predominant role of right hemisphere lesions in the aetiology of unilateral neglect or hemi-inattention is still unexplained (Friedland and Weinstein, 1977). While minor attentional deficits for the contralateral half of space may follow injury to either cerebral hemisphere, the characteristic syndrome of pronounced unilateral neglect for one half of surrounding space or of the body itself is most frequently produced by lesions of the right hemisphere in right-handed patients (Friedland and Weinstein, 1977; Heilman and Watson, 1977*a*, *b*; Hécaen and Albert, 1978). Proposed explanations generally assume that the functional loss within the damaged right hemisphere is a sufficient basis for the disorder (Lhermitte, 1939; Brain, 1941; McFie *et al.*, 1950; Denny-Brown *et al.*, 1952; Hécaen and de Ajuriaguerra, 1952; De Renzi *et al.*, 1970; Gainotti *et al.*, 1972; Heilman and Watson, 1977*a*, *b*; Geschwind, 1981). It is tacitly implied that the undamaged left hemisphere by itself has no

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capacity for awareness of the left side. Some recent interpretations (Kinsbourne, 1970; Heilman and Watson, 1977*a*, *b*; Heilman and Valenstein, 1979; Heilman and Van Den Abell, 1980) suggest that hemi-inattention may result from a 'hypo-aroused' or 'hypo-activated' state of the damaged right hemisphere relative to the intact left hemisphere, the latter therefore assuming control of behaviour. In these models it is also assumed that the left hemisphere is intrinsically unable to attend to the left half of space and of the body.

The absence of significant hemineglect following right hemispherectomy (Smith, 1969, 1972), however, and also following forebrain commissurotomy (Sperry *et al.*, 1969; Joynt, 1977) would seem to indicate, in contradiction to the foregoing, that the left hemisphere, under these conditions at least, has the ability to attend to both sides of the body and of extrapersonal space. In line with this, it is difficult to understand how the intact cognisant left hemisphere of an alert and linguistically competent patient would fail to notice blunders such as repeatedly raising the right arm instead of the left, grooming only the right half of the body or ignoring the contents of the left half of a dinner plate (Hécaen and de Ajuriaguerra, 1952; Oxbury *et al.*, 1974; Gardner, 1976; Heilman and Watson, 1977*b*). Equally difficult to reconcile with the known capacities of an intact left hemisphere is the tendency to represent in drawing only the right half of an object and the peculiar reluctance to correct omissions when they are pointed out, as well as the frequent association with certain other behavioural disorders (Weinstein and Friedland, 1977).

It would thus appear that more is involved than a mere loss of right hemisphere functions, and that the processing in the intact left hemisphere is also affected at a cognitive level. The symptoms and evidence relating to lateral neglect are in conformance, overall, with the possibility that (1) the left hemisphere possesses adequate mechanisms for attending to, and acting in, both halves of space, but that (2) those mechanisms mediating left-sided awareness are subject to differential suppression in the presence of the cerebral commissures *via* disruptive influences from a focally damaged right hemisphere. To explore this hypothesis further in the present study we tested the left hemisphere for left-sided awareness in commissurotomy subjects in whom there are more reliable means for determining directly, through lateralized testing, what capacities are present in each hemisphere.

As a general rule, commissurotomy subjects have shown little or no hemineglect under conditions of unrestricted, nonlateralized testing (Sperry *et al.*, 1969). With lateralized tests examples of hemineglect are, of course, evident among disconnection phenomena. These differ, however, from the classical neglect syndrome in that they are readily accounted for by commissure section, occur in either hemifield without preference, and do not seem to involve the kinds of cognitive loss described above. In the present tests we have focused on the assessment of the left hemisphere capacity for localization of left bodily parts and for performing a line bisection test.

METHODS

Subjects

The study was conducted with three subjects (L.B., N.G., R.Y.) who had undergone presumed complete surgical section of the corpus callosum along with the anterior and hippocampal commissures. The surgery had been carried out fifteen, seventeen and fourteen years earlier, respectively, for relief of intractable epilepsy. L.B. and N.G. are thought to have the least amount of extracallosal brain damage even though no localized lesion could be found in R.Y. The individual case histories are presented in further detail elsewhere (Bogen *et al.*, 1965; Bogen and Vogel, 1975).

Left Hemibody Neglect

The test procedures were based on the tendency of hemiasomatognostic patients to make errors such as raising the right arm when requested to raise the left or both arms, or touching the right ear when requested to touch the left or both ears (Hécaen and de Ajuriaguerra, 1952; Critchley, 1953; Fredericks, 1969; Friedland and Weinstein, 1977; Heilman and Watson, 1977*b*; Hécaen and Albert, 1978). In the present study similar requests were made to commissurotomy subjects in a manner such that only the left hemisphere received the instructional information indicating which command to perform. The instructional inputs were presented first in the tactile modality and, later in separate tests, in the visual modality.

Testing procedures for tactile input. On each trial one of the three plastic capital letters R, L, or C, 5 cm high, was placed in reach of the left or right hand of the subject for tactile identification out of sight behind a screen. The subject was instructed orally that he was to execute a certain command that would involve, on a given trial, performance either on the right side, the left side, or the centre of his body, depending on whether the plastic cut-out letter R, L or C, respectively, was presented. Blind palpation of the letter with one hand ensured that only the contralateral hemisphere received sufficient information to determine the task instruction. The subject was instructed not to speak during the testing and the wrist of the subject was held firmly against the table to eliminate cues from proximal arm and shoulder movement during the process of manual palpation. Trials were presented in blocks of 30 with each instruction letter appearing ten times per block in a pseudorandom order.

Individual subjects participated in four or more testing sessions conducted at least two days apart. In the first of the test series, subjects were instructed to respond by pointing to the right ear, left ear or chin when the letter R, L or C was presented. The hand used for pointing was the same as that used for identification of the instructional letter. The right hand was used first for a block of 30 trials, followed by the left hand on a different randomized sequence of 30 trials. The same procedure was repeated in another session in order to obtain 60 trials for each hand.

In the second test series, the subjects were instructed to respond by raising the right arm, the left arm, or by tapping the centre of the table in front of them when the letter presented was R, L or C, respectively. Otherwise the procedures were the same as those used in the first series, except that the instructional sequences were varied. The test tasks were designed to be sufficiently simple that failures could not easily be attributed to the task complexity or to inability to comprehend the general instructions.

Control trials were conducted before and after the test series described above to ascertain that the information necessary for tactile identification of the latter remained available only to one hemisphere, that is, to the hemisphere contralateral to the hand used for palpation. In the control trials the subject was required to identify by palpation a letter, presented as above, and then to retrieve the letter among the three possible choices by using either the ipsilateral or contralateral hand. At least 45 trials were presented to each hand for each retrieval condition.

Testing procedures for visual input. The subject, seated at a table in front of the tachistoscope (Gerbrands Model No. T2BC coupled with a timer), was told to hold his gaze on a central fixation point on the screen. Three words were then flashed in quick succession comprising a simple command to be obeyed, such as 'Raise your hands', or 'Touch both ears'. Each word was exposed for 150 ms to the right of the fixation point. Table 2 shows the commands which were used, in the order of presentation. It has been generally established that commissurotomy subjects are not able to obey verbal commands presented in this manner to the left visual field. This was used to evaluate the adequacy of the input lateralization by running control trials at the end of the session with the same words presented in the same way to the left visual field.

Stimulus cards consisted of rectangular pieces of white cardboard on which the word to be presented was printed in black capital letters. Each word, presented horizontally, subtended a visual angle of 2.5 to 5 deg depending on the number of letters. The medial edge of each word was placed 1 deg off the field centre. Three exposures, a few seconds apart, were required for each command. The subject's dominant (right) eye, with visual acuity at least equal or corrected to 20/25, was used for stimulus viewing, the other being covered with a patch. Just before the presentation of each word, the examiner said 'ready' to warn the subject to maintain fixation carefully. Two practice instructions ('touch your nose'; 'close your eyes') were given to acquaint subjects with the procedure. Nothing was said beforehand about the instructions except that they consisted of three words and the subjects were asked to refrain from speaking during the testing. The same procedure was repeated with left visual field presentations.

Hemispatial Neglect

Both disconnected hemispheres were tested independently for evidence of contralateral neglect. The line bisection test (Critchley, 1953) as modified for blind tactile performance (Bowers and Heilman, 1980) was used to obtain lateralization to left and right hemispheres. The test was presented to both hands for synchronous performance in order to occupy each hemisphere fully and prevent crossing of information or output. Two wooden rods of unequal length, varying from 12 to 24 cm, were presented out of sight one to each hand and the subject's task was to estimate the midpoint of each stimulus with the corresponding hand. The subject was instructed to run the index finger of each hand along the corresponding stimulus as many times as desired, but to move both hands in synchrony and to indicate with the left and right index fingers simultaneously the estimated midpoint of both stimuli. When the subject occasionally failed to use both hands in synchrony, the trial was not scored and had to be repeated correctly. With strict adherence to this requirement, it could be assumed that the results obtained with each hand reflected processing by the contralateral hemisphere.

Stimuli and procedures. The rods were made of half-round moulding (1.5 cm wide) cut to five different lengths (12, 15, 18, 21 and 24 cm). This allowed 20 pair permutations combining stimuli

TABLE 1. RESULTS OF TACTILE INPUT TESTS†

Instruction		*Pointing to R. ear, L. ear, or chin*		*Raising R. arm, L. arm or tapping table*	
Hand used for letter palpation		*Right*	*Left*	*Right*	*Left*
Total number correct (maximum 60)	N.G.	58*	16 n.s.	59*	26 n.s.
	R.Y.	53*	21 n.s.	56*	20 n.s.
No. correct with 'R' (maximum 20)	N.G.	20	4	20	9
	R.Y.	19	8	19	4
No. correct with 'L' (maximum 20)	N.G.	20	5	19	7
	R.Y.	20	12	19	14
No. correct with 'C' (maximum 20)	N.G.	18	7	20	10
	R.Y.	14	1	18	2

Symbols: * $P < 10^{-4}$; n.s. nonsignificant, $P > 0.1$; † L.B. excluded from analysis (*see text*) of unequal length. Both stimuli were fixed in line on the longitudinal axis of a rectangular piece of cardboard (71 × 8 cm) with the other end of each stimulus placed 10 cm from the corresponding end of the cardboard. The 20 stimulus pairs were presented to the subject in a pseudorandom sequence which was used for all testing sessions. The subject was never allowed to look at the stimuli. The subject sat blindfolded at a table and performed all trials with hands uncrossed. Stimulus cards were presented horizontally flat on the table. At the start of each trial, the subject's index finger was placed at the outer end of the corresponding rod. The task was performed under four different conditions depending upon the position of the stimuli in relation to the midline of the subject's body. In condition 1, both stimuli were placed to the right of the subject who executed the task with both hands in the right hemispace. In condition 2, both stimuli were placed to the left of the subject who executed the task with both hands in the left hemispace. In condition 3, the stimulus for the right hand was placed at centre directly in front of the subject and the stimulus for the left hand was placed to the left of the subject. In condition 4, the stimulus for the left hand was placed at the centre and the stimulus for the right hand was placed to the right of the subject. Each subject completed two blocks of 20 stimuli in each condition. One practice trial preceded each block. Four testing sessions were required for each subject and the order of stimulus location was counterbalanced across sessions. The distance between the estimated and actual midpoints was measured to the nearest centimetre for each hand and was expressed as a percentage of the length of the corresponding rod. The percentage was given as + or − score depending on whether the deviation was toward the subject's right or left side, respectively.

RESULTS

Neglect of Left Hemibody

Tactile input. The results are summarized in Table 1. When using the right hand (left hemisphere input) for palpation of the letters, the subjects gave appropriate responses in a high proportion of the trials performing at a level far beyond chance prediction ($P < 10^{-4}$) (Tables of the Cumulative Binomial Probability Distribution, 1955). Inspection of the numbers of correct trials for each letter reveals that the subjects responded as well following palpation of the letter 'L' as following palpation of the letter 'R' and thus on these tests did not exhibit any tendency to ignore the left side of the body.

In sharp contrast, the subjects' performance failed to rise above chance level when they used the left hand (right hemisphere input). R.Y. tended to respond more often on the left side than on the right, and therefore gave many (12 and 14) correct responses on trials with the letter 'L'. His overall performance, however, remained at chance level. It is not possible here to determine whether the subjects' failure with the right hemisphere resulted from inability to associate the appropriate instruction with a given letter or from other possible causes. However, this is not of direct concern since the aim of the tests was to evaluate left hemisphere capacity in isolation.

In control trials ipsilateral retrieval was performed correctly at levels of 85 per cent or higher whereas with contralateral retrieval, the percentage of correct responses fell to less than 45 per cent for N.G. and R.Y. (chance level is 33 per cent), but remained about 90 per cent for L.B. These figures confirm that the instructional input was adequately lateralized in N.G. and R.Y. In L.B., however, who is noted for exceptional development of cross-integrative strategies, the control tests indicated that the instructions were not being adequately lateralized and therefore L.B. has been excluded from the analysis.

Visual input. Table 2 shows the results obtained with right visual field presentations. Following commands that called for only one bodily part to be moved or pointed to, the subjects gave correct responses in all but one instance and showed no evidence of neglect of the left hemibody; in conformance with the results obtained with tactile input.

When the command specified two (homotopic) bodily parts, N.G. and R.Y. showed evidence of some left hemibody neglect, ranging from slight delay in the onset of response to complete absence of response. Most omissions occurred following the rather ambiguous commands employing the word 'your' instead of

TABLE 2. RESPONSES FOLLOWING RIGHT VISUAL PRESENTATIONS

	Responses		
Commands	*R.Y.*	*N.G.*	*L.B.*
Raise your hands	Omission left	C	C
Touch your ears	Omission left	C	C
Touch your knees	Omission left	Omission left	C
Show your thumbs	Omission left	Delay left	C
Show your elbows	Omission left	C	C
Raise both hands	Omission left	C	C
Touch both ears	C	C	C
Touch both knees	Delay left	Delay left	C
Show both thumbs	Omission left	C	C
Show both elbows	C	C	C
Touch left ear	C	Opposite	C
Touch right ear	C	C	C
Show right thumb	C	C	C
Raise right hand	C	C	C
Raise left hand	C	C	C
Touch left elbow	C	C	C
Touch left knee	C	C	C
Show left thumb	C	C	C
Touch right knee	C	C	C
Touch right elbow	C	C	C

C = correct response. Delay = trials requiring response on both sides and in which response on side indicated after 'Delay' was slower and less affirmative than on the other side. Omission = trial requiring response on both sides and in which the subject failed to respond on side indicated after 'Omission'. Opposite = trial in which subject responded on side opposite to that specified by instruction. These four categories of responses are mutually exclusive.

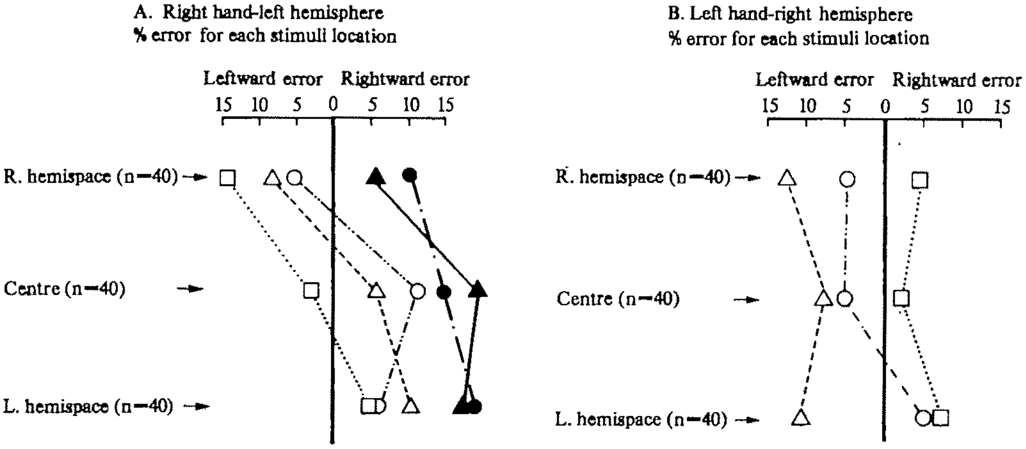
'both', indicating that the mild neglect observed tended to disappear following more explicit instructions. These minor manifestations of neglect are more characteristic of the parietal akinesia observed following damage to either parietal lobe (Critchley, 1953) than of the kind of neglect typical of right hemisphere lesion.

In control trials presented to the left visual field, N.G. and R.Y. characteristically failed to respond and vocally denied having seen any word. L.B., on the other hand, reported having seen something but was unable to carry out the commands. These findings confirm that the instructional input was adequately lateralized in all three subjects.

Hemispatial Neglect

Results of the rod bisection test for awareness in extrapersonal space are presented in fig. 1, A and B, for the right and left hand, respectively. Subjects made substantial errors in estimating the midpoint of the rods. The magnitude of errors was comparable for both hands when subjects were pooled. The direction of errors appeared, however, to be influenced differently for each hand. For the left hand, the direction of errors changed with the subjects rather than with the location of stimuli; thus N.G. always erred to the left, R.Y. always to the right. In contrast, all three subjects tended with the right hand to err towards the body midline (i.e. to the left in right hemispace and to the right in the left hemispace) and thus seemed influenced by the location of stimuli. It is not clear how this difference between hands or hemispheres could be related to the classical phenomenon of spatial neglect.

Because of low accuracy in the execution of the task and of the absence of clear manifestations of unilateral neglect, adequate interpretation of the data required further knowledge as to how lesion patients with classical left hemineglect would



A. Right hand-left hemisphere
% error for each stimuli location

B. Left hand-right hemisphere
% error for each stimuli location

FIG. 1A and B show mean distance (% rod length) between the estimated and actual midpoints for each stimulus location (40 trials) for the right and left hand, respectively. Standard errors are roughly equal to the width of the symbols. Results of two patients (N1, N2) with left unilateral neglect caused by right hemisphere damage are also included in A for comparison. R.Y. = □; N.G. = △; L.B. = ○; N1 = ▲; N2 = ●.

perform the rod bisection test used above. We therefore administered this task to 4 right-handed patients who had sustained right hemisphere damage. The diagnoses were fronto-temporo-parietal infarction in N1 and N2, and parieto-occipital tumour and parietotemporal infarction in the two other patients. The procedures were exactly the same as above except that patients used only the right hand. Two patients (N1, N2), whose results are depicted in the fig. (A) showed a typical left unilateral neglect. In contrast to the right hand performance of commissurotomy subjects, they always erred to the right of the actual midpoint irrespective of the location of stimuli. (The 2 other patients made errors of 5 per cent or less for all stimuli locations showing no significant side preference. They were more accurate than commissurotomy subjects, presumably because they had to bisect only one rod at a time rather than two concurrently as required for commissurotomy subjects.) For all stimuli locations, there was a significant difference between the pooled right hand results of commissurotomy subjects and those of N1 and N2 (Scheffé *post hoc* comparisons, df = 4,195, $P < 0.001$) (Roscoe, 1975).

The results indicate that lesions of the right hemisphere can induce on a rod bisection task a pattern of constant errors to the right that is not observed when commissurotomy patients execute the same task under left hemisphere control. The left disconnected hemisphere data revealed no evidence of left hemineglect as seen here following right hemispheric lesions.

With the left hand-right hemisphere L.B. and R.Y. likewise revealed no evidence of right hemineglect but N.G. showed large and consistent deviation to the left which might be interpreted as a right hemineglect. This last observation is not a major concern, however, since it has not been noted with the two other patients and since the present aim was to verify whether the characteristic predominance of right hemispheric lesions in producing left-sided neglect arises from an intrinsic inability of the left hemisphere.

The data were also analysed to verify an assumption that commissurotomy subjects were executing the task with each hand-hemisphere system independently. Lack of independence between both hands would presumably show up in greater errors for trials in which the length difference between both rods was large. However, no correlation between the magnitude of errors and the length difference between rods was found, suggesting that the test was executed with each hand independently.

DISCUSSION

The present findings show that commissurotomized subjects given instructional input restricted to the left disconnected hemisphere execute correctly commands involving the left hemibody, exhibiting only negligible, if any, left hemibody neglect no greater than the mild akinesia observed to follow injury to either parietal lobe (Critchley, 1953). The subjects also failed to reveal consistent evidence of unilateral neglect for the left half of surrounding space when tested with a rod bisection task executed independently by each hemisphere. Control tests showed that the inputs had been adequately lateralized and that the results reflected the performance of the unassisted left hemisphere. L.B. and N.G. likewise revealed no evidence of contralateral neglect when choosing answers for the Raven's Matrices presented visually to either hemisphere by a special optical device (Zaidel *et al.*, 1981).

In contrast to the outcome after unilateral lesions (Heilman and Watson, 1977*a*; Hécaen and Albert, 1978), the present findings indicate that the left hemisphere possesses substantial awareness for the left half of the body as well as for the left half of objects and surrounding space. We infer that the left hemisphere functioning independently possesses the requisite intrinsic cognitive mechanisms needed to prevent the appearance of the typical neglect syndrome of right hemispheric lesions (Hécaen and de Ajuriaguerra, 1952; Critchley, 1953; Fredericks, 1969; Friedland and Weinstein, 1977; Heilman and Watson, 1977*b*; Hécaen and Albert, 1978; Schenkenberg *et al.*, 1980).

Two possible objections concerning the foregoing interpretations require comment. First, it might be conceivable that the left hemisphere capacity for left side awareness was acquired only after the commissurotomy through gradual functional readaptation. This seems highly unlikely because the subjects from the start showed only minimal or no evidence of neglect even in the early postoperative period when their behaviour appeared to be mostly under left hemisphere control (Sperry *et al.*, 1969). Secondly, the neurological status of our subjects may not be representative of the normal state because of the effects of early brain damage and longstanding intractable epilepsy. This objection cannot be directly refuted but its relevance to findings such as those of the present study has so far not been substantiated. Repeated observations have revealed that the commissurotomy subjects exhibit a pattern of functional dichotomy between the right and left hemispheres that correlates well with data from hemispherectomy.

The results are taken to support the conclusion that the syndrome of unilateral neglect cannot be explained solely in terms of right hemisphere dysfunction, and thus suggest a revision in past interpretations that have focused uniquely on right hemisphere pathology in explaining the neglect syndrome. If the left hemisphere by itself possesses adequate compensatory capacities to prevent the characteristic cognitive and conceptual symptoms of neglect, as the present findings indicate, it would seem to follow that the function of these awareness mechanisms in the left hemisphere must be disrupted also by the right-sided lesions. This does not apply however to the minor manifestations of inattention, such as unilateral akinesia or sensory extinction, observed following damage to either cerebral hemisphere (Critchley, 1953) and which appear to be ascribable to disturbances limited to the involved hemisphere.

The idea that unilateral neglect is best accounted for in terms of bilateral cerebral dysfunction was first expressed, although in a different context, by Battersby *et al.* (1956). They suggested that the disorder resulted from the combined effects of defective sensory input and general mental deterioration. This interpretation has since been criticized because patients with typical neglect occasionally show no demonstrable sensory loss and frequently do not suffer from a degree of general mental deterioration sufficient to account for the marked cognitive disturbances (Hécaen, 1962; Oxbury *et al.*, 1974; Gardner, 1976). Nevertheless the collective evidence supports the presence of a bilateral cerebral dysfunction in neglect (Friedland and Weinstein, 1977; Weinstein and Friedland, 1977). Although Heilman and colleagues described bilateral but asymmetrical arousal defects in patients with neglect, they did not consider bilateral hemispheric dysfunction of primary importance in causing the neglect phenomenon in itself (Heilman *et al.*, 1978).

It thus appears that the search towards a full understanding of the neglect syndrome must include the study of the interactions and divisions of tasks between the hemispheres in addition to that of the individual capabilities of the right and left hemispheres. Our present evidence supports an interpretation along the following lines. (1) With the cerebral commissures intact, the two hemispheres may be assumed normally to work together as an integral unit (Sperry, 1977). (2) Each hemisphere probably has a capacity for exploration and representation of both sides of space. (3) The right hemisphere appears to play a leading role for cognitive operations that involve spatial relationships (*for review, see* Hécaen and Albert, 1978) as well as for certain attentional tasks (Howes and Boller, 1975; Umiltà *et al.*, 1979). Further evidence indicates that the electroencephalographic activity (spectral frequency analysis) of the right hemisphere is modified following detection of stimuli from either visual fields, whereas that of the left hemisphere is solely influenced by right visual field stimuli, supporting the contention that the right hemisphere is involved in surveying both sides of surrounding space (Heilman and Van Den Abell, 1980). (4) Where cerebral asymmetry of function has thus evolved (to avoid conflict, interference, to utilize available neural space effectively . . .) damage to the hemisphere predominantly responsible for a particular function disrupts the functioning of the entire system and thus interferes with the expression of compensatory abilities in the intact as well as in the damaged hemisphere. For left hemineglect from right-sided lesions, the leading role of the lesioned right hemisphere may be preserved even though specific spatial and attentional functions are lost with the result that the left hemisphere is suppressed and unable to exert the intrinsic potential that is present as observed in these tests.

Why then do right hemispheric lesions not cause bilateral neglect? Although it is true that right-sided lesions are not followed by severe right-sided neglect (probably because the sensory information directly conveyed to the left hemisphere is sufficiently processed to prevent such occurrences), there are indications that right-sided lesions can produce minor attentional or exploratory deficits within the right side of space (Chédru *et al.*, 1973). That study revealed that, in the absence of visual field defects, patients with right-sided lesions had visual searching times that were increased similarly for right and left placed targets, whereas patients with left-sided lesions showed increased search times only for right-sided targets.

Further work is required as the focus of this study was not directed at that particular topic.

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SPECIFIC RECEPTORS FOR CALCITONIN IN THE SUBFORNICAL ORGAN OF THE BRAIN

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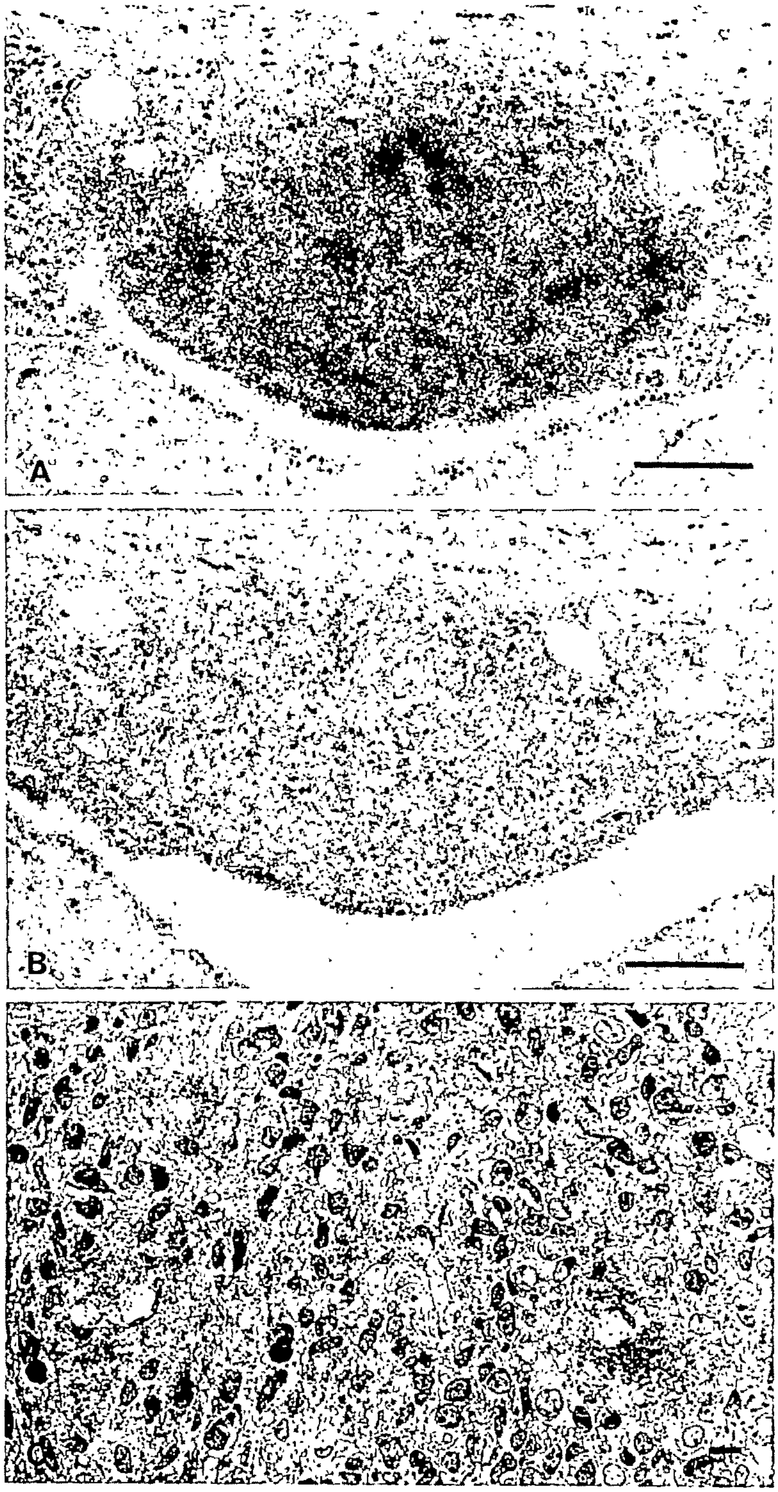
SUMMARY

A radioautographic method was used to locate specific binding sites for biologically active iodinated calcitonin in rats. The results show that the subfornical organ of the brain, a suspected water regulating organ, is a specific target for calcitonin. The hormone predominantly binds to processes of tanycytes, suggesting that these ependymal cells play an intermediate role between the endocrine and nervous systems.

INTRODUCTION

A large number of tissues have been surveyed using an *in vivo* method to localize binding sites for the hormone calcitonin. Quantitative radioautography with iodinated salmon calcitonin (^{125}I-sCT) has shown specific and saturable binding to the membranes of osteoclasts in bone and to the adluminal surface of certain portions of the uriniferous tubules in the kidney (Warshawsky *et al.*, 1980). In this paper the presence of specific receptor sites for calcitonin within the subfornical organ of the brain is reported.

Since its discovery (Smith, 1898) the precise role of the subfornical organ has not been resolved. Pines (1926) named this structure after observing it in numerous animals including man (Pines and Maiman, 1928). The organ is highly vascularized, richly innervated, and contains a variety of glial cells and their processes (Akert, 1969). It occupies a strategic position in the dorsal wall of the third ventricle, being closely related to the fornix, the commissural fibres and the nucleus triangularis. This circumventricular organ has been variously implicated as a neurosecretory organ (Leonhardt and Lindemann, 1973), a receptor for chemical stimuli from the cerebrospinal fluid (Buranarugsa and Hubbard, 1979), and an osmoreceptor (Dierickx, 1962). Recent data suggests that calcitonin may elicit some actions through the nervous system. Indeed, when injected into the cerebral ventricles, calcitonin has an inhibitory effect on eating in rats (Freed *et al.*, 1979) and suppresses gastric acid secretion (Morley *et al.*, 1981). Although the subfornical organ has not been directly related to the feeding centre, it has been shown that it has neural projections to the supraoptic nucleus of the hypothalamus (Miselis *et al.*,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1979), a structure known to be involved with maintenance of water balance (Carpenter, 1978) and in which saturable receptors for angiotensin have been found (van Houten *et al.*, 1980).

MATERIALS AND METHODS

In all experiments performed, male Sherman rats of approximately 100 g were injected intravenously with freshly iodinated salmon calcitonin (^{125}I-sCT) prepared according to the chloramine T method and tested for biological activity (Warshawsky *et al.*, 1980). *Experimental animals* were injected with ^{125}I-sCT. After 2 min of systemic circulation, unbound hormone was washed out by an intracardiac perfusion of Ringer-lactate solution. Bound hormone was subsequently fixed by perfusion with 2.5 per cent glutaraldehyde in 0.05 M Sorenson's phosphate buffer (Warshawsky *et al.*, 1980). *Control animals* were injected with an identical amount of ^{125}I-sCT mixed with an approximately 500-fold excess of the same unlabelled hormone. In experiments numbered 1, 2 and 3, experimental rats received 0.119, 0.246 and 0.124 μg of ^{125}I-sCT with a specific activity of 645, 735.5 and 712.1 μCi/μg, respectively. The controls received the same amount of labelled hormone mixed with 50, 125 and 80 μg, respectively, of unlabelled sCT. In experiment 3, an additional animal was injected with 0.124 μg of ^{125}I-sCT mixed with 150 μg of unlabelled angiotensin II.

Light microscope radioautographs were prepared according to Kopriwa and Leblond (1962) and electron microscope radioautographs according to Kopriwa (1973).

RESULTS

The radioautographic reaction due to binding of ^{125}I-sCT was intense over the subfornical organ in paraffin embedded cross sections of the brain obtained from experimental animals (fig. 1A) but weak over the sections obtained from the controls where labelled calcitonin was mixed with an excess of unlabelled hormone (fig. 1B). Examination of 0.5 μm thick Epon sections showed that the reaction predominated over the perivascular tissue of this organ (fig. 1C). Electron microscope investigation of this particular area indicated the presence of a variety of ependymal tanycyte and glial cell processes, as well as dendrites, axons and axon terminals. The electron microscope radioautographs showed that silver grains were associated with the cytoplasmic membranes of the structures found in this region (figs. 2A, B). Although the mixture of different cell processes made it difficult to assign the label, processes of the ependymal tanycytes were always present in labelled regions. Since silver grains were most frequently seen over those areas exclusively composed of tanycyte processes (fig. 2B), it was concluded that tanycyte membranes are the specific targets for calcitonin.

FIG. 1 (*opposite*). Light microscope radioautographs of the subfornical organ. A, paraffin section (4 μm thick) from an experimental animal. Experiment 1 (× 140; bar = 100 μm). B, similarly exposed radioautograph obtained from the control animal. (× 140; bar = 100 μm). Note the high concentration of silver grains over regions of the organ in the experimental (A) compared to the absence of grains over the control (B). C, Epon section (0.5 μm thick) of the subfornical organ parenchyma of an experimental animal. Experiment 2. (× 365; bar = 10 μm). The high resolution provided by this semithin section permits localization of the grains to the perivascular tissue of the organ.

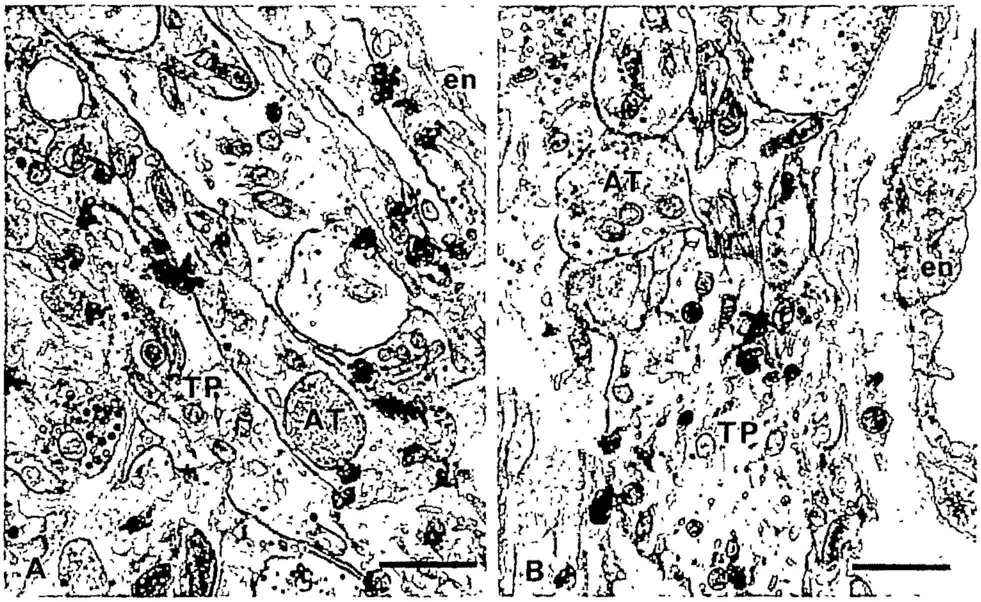

FIG. 2. Electron microscope radioautographs of subfornical organ perivascular tissue obtained from an experimental animal, Experiment 2 (× 12187; bar = 1 μm). A, numerous cell processes including axon terminals (AT) are seen closely related to the blood vessel endothelial cells (en). Most silver grains overlie the membrane of tanycyte processes (TP). B shows the selective labelling associated with the membrane of a tanycyte process.

The qualitative observations of experiment 1 were substantiated by counting silver grains in two subsequent experiments (2 and 3). In each case 10 counts were made over 0.001 mm^2 of tissue. In experiment 2, an average of 1509 grains (SD ± 970; SEM ± 307) were counted over Epon sections obtained from the experimental rat compared to 226 grains (SD ± 45; SEM ± 14) counted over a similar area in sections obtained from its accompanying control ($P < 0.001$, Student's t-test). In experiment 3, 563 grains (SD ± 99; SEM ± 31) were counted over paraffin sections from the experimental animal compared to 59 grains (SD ± 8; SEM ± 2) in the control ($P < 0.001$ Student's t-test). An additional control animal was injected with ^{125}I-sCT mixed with an excess of unlabelled angiotensin II to test for competitive binding. A total of 469 grains (SD ± 1·12; SEM ± 36) were counted from sections obtained from this animal as compared to 563 grains over the experimental ($P < 0.05$ Student's t-test).

DISCUSSION

Radioautography of paraffin-embedded cross sections of the entire rat brain at the level of the subfornical organ revealed this organ to be the only labelled site. No other structures in the sections were labelled after injection of labelled calcitonin.

Other studies have shown binding to other paraventricular regions of the brain (van Houten *et al.*, 1982) but not to other brain structures.

The high concentration of silver grains over focal regions of the subfornical organ in the experimental rats, compared to the nearly total absence of grains over the control animals is due to the competition between the small amount of radioactive and large amount of nonradioactive hormone available to the saturable binding sites. The fact that large amounts of unlabelled angiotensin II did not compete significantly for calcitonin binding sites suggests that the sites are specific for calcitonin and that angiotensin has separate receptors within the subfornical organ.

The results of the present investigation indicate that the subfornical organ is the site of competitive, saturable binding for the hormone calcitonin and that the cells binding the hormone are ependymal, presumably tanycyte in nature. Much of the classical work on the action of calcitonin was based on its ability to regulate blood calcium levels (Foster *et al.*, 1972), thought to be mediated by inhibition of osteoclastic bone resorption (Lucht, 1973; Holtrop *et al.*, 1974). Whether this is its sole function is still uncertain, particularly in view of the facts that calcitonin is found in cartilagenous fish that do not possess a bony skeleton (Copp, 1972) and, in humans, high levels of calcitonin associated with malignant tumours of the calcitonin-producing cells of the thyroid (Hill *et al.*, 1973) and low levels of calcitonin produced by thyroidectomy cause little alteration in the blood calcium level. Alternatively, recent work has linked this hormone to the central nervous system. Calcitonin-like immunoreactivity has been found in the nervous system of certain protochordates (Fritsch *et al.*, 1979; Girgis *et al.*, 1980), and in the pituitary gland of various mammals (Deftos *et al.*, 1978; Cooper *et al.*, 1980). Endogenous calcitonin has been identified in extracts of brain (Fischer *et al.*, 1981) and the hormone binds to particulate cell fractions from the brain (Nakamuta *et al.*, 1981; Rizzo and Goltzman, 1981). Additionally, when calcitonin is injected into the cerebral ventricles, it elicits a variety of physiological responses (Freed *et al.*, 1979; Morley *et al.*, 1981). Therefore it seemed reasonable to suspect that this hormone may have a site of action within the brain. Indeed this study has demonstrated specific binding sites for calcitonin within the subfornical organ.

The subfornical organ has already been shown to contain specific binding sites for angiotensin II (van Houten *et al.*, 1980) and electrophysiological studies have shown that application of this hormone to the subfornical organ initiates the propagation of action potentials in its neural components (Buranarugsa and Hubbard, 1979). Intravenous and intraventricular injection of angiotensin II, as well as direct application of this hormone to the subfornical organ, all elicit drinking behaviour in rats (Simpson *et al.*, 1978). Thus the subfornical organ seems to be involved in water balance. Calcitonin, because it acts on the kidney (Bijvoet *et al.*, 1972), has also been implicated in water balance. Hence, it is reasonable to suggest that calcitonin as well as angiotensin II may both be involved with the subfornical organ in water balance and related electrolyte homeostasis. However, whether it does so by eliciting drinking behaviour, such as does angiotensin II, has been questioned (Freed *et al.*, 1979). Other possible actions of calcitonin manifested *via* the brain have also been documented; when injected intraventricularly, this hormone has an inhibitory effect on eating (Freed *et al.*, 1979) and it also affects the level of gastric secretion (Morley *et al.*, 1981).

The structural complexity of the subfornical organ (Akert, 1969), its numerous central nervous system projections (Miselis *et al.*, 1979), and the fact that it is a target tissue for a variety of hormones (angiotensin, van Houten *et al.*, 1980; insulin, van Houten *et al.*, 1979) support the idea that this organ may function in the neuronal modulation of a variety of physiological responses some of which involve the nonskeletal action of calcitonin.

The observation that saturable binding of the hormone calcitonin occurs on the membrane of tanycytes in the subfornical organ suggests a special role for these cells. In the median eminence ependymal tanycytes are linked to nervous tissue by synaptoid contacts (Scott and Willis, 1979; Rodríguez *et al.*, 1979). The target cells for calcitonin within the subfornical organ may also be related to neurons by such connections. If so, tanycytes could be visualized as ependymal cells that play an intermediate role linking the endocrine to the nervous system.

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RECORDING OF AUDITORY EVOKED POTENTIALS IN MAN USING CHRONIC SUBDURAL ELECTRODES

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SUMMARY

With the aid of chronic subdural electrodes we have been able to record from the posterior banks of the sylvian fissure, auditory evoked potentials (AEPs) that had morphologies and peak latencies compatible with the primary AEPs described by Celesia and Puletti (1969). These AEPs had amplitudes that were not only affected by the side of stimulus presentation but were maximal in an area close to the primary auditory cortex. The AEPs also displayed an extremely steep spatial gradient and were not altered by pentobarbitone sodium and nitrous oxide anaesthesia. Together, these properties suggest that these subdurally recorded potentials are near-field evoked potentials from the primary auditory cortex. The focal nature of these potentials also allows them to be used as effective electrophysiological tools for localization of the primary auditory cortex in patients.

INTRODUCTION

Since its introduction in the midforties the technique of electrical stimulation for localization of cortical speech areas has been widely used in temporal lobe surgery to define the posterior boundary of resection in the dominant lobe (Penfield and Roberts, 1959; Ojemann, 1979). This procedure is conducted intraoperatively and employs the concept that electrical stimulation of the speech cortex results in transient interference of voluntary speech. At our institution, cortical stimulation is conducted preoperatively with the aid of a chronic subdural electrode array. This electrode system has the distinct advantage of allowing the stimulation procedure to be carried out in a systematic and comprehensive fashion outside the stressful environment of the operating room (Lesser *et al.*, 1981; Lueders *et al.*, 1982). While working with this system, we observed that in 5 patients, the temporal speech areas as defined by electrical stimulation, were close to and apparently posterior to the approximate anatomical location of Heschl's gyri, which lie buried within the sylvian fissure. The proximal relationship of the temporal speech area to Heschl's gyri seems a logical one since it would facilitate rapid transfer of incoming auditory information from the primary auditory cortex to the adjacent temporal speech cortex for further processing. If such a spatial relationship is indeed a consistent finding in human subjects, it would greatly expedite the task of defining the speech area. In order to verify this observation, it is essential that we be able to devise an accurate method for localizing Heschl's gyri or more specifically, the primary auditory cortex, which occupies a large portion of these gyri in man (Brodal, 1981).

A much used electrophysiological technique for identification of the primary auditory cortex in animals involves the detection of electrical potentials evoked in the primary sensory area by auditory stimulation (Ades and Felder, 1942; Woolsey and Walzl, 1942; Tunturi, 1944; Pribram *et al.*, 1954; Kaga *et al.*, 1980). Recently, a similar technique was employed by Celesia and Puletti (1969) to map the primary auditory cortex in man. This task necessitated the use of multicontact depth electrodes inserted into the supratemporal plane within the sylvian fissure. Whether the primary auditory evoked potentials (AEPs) can be detected from outside the fissure is not well established. The routine use of chronic subdural electrodes at our institution in candidates for temporal lobectomy provided us with the rare opportunity to record AEPs from the perisylvian region, and also determine whether primary AEPs are volume-conducted to this area. In this paper, we will present evidence to show that primary AEPs can indeed be recorded from the banks of the sylvian fissure and, additionally, can be used to localize precisely the primary auditory cortex. A detailed description of the neurophysiological characteristics of the volume-conducted primary AEPs will be provided. A future report will deal with the special relationship of the temporal speech area to the primary auditory cortex.

METHODS

This study involved 5 patients with intractable complex partial seizures, aged 11 to 29 yrs (mean 21), admitted to the Cleveland Clinic as candidates for temporal lobectomy. The major epileptic foci were on the left side in 3 patients, and on the right in 2. Standard temporal craniotomies were performed on the appropriate side in the 5 patients for implantation of the subdural electrode arrays. Following the incision of the dura, the electrode arrays were placed over the mid and posterior perisylvian region, covering much of the superior aspect of the temporal lobes in all 5 cases. Their locations relative to the tip of the temporal lobe were measured at the time of operation. Before closure, the electrode arrays were sutured to overlying dura in order to prevent slippage.

Informed consent was obtained from all patients or their parents for participation in this study. AEPs were recorded with patients in the supine position. They were in stage I or II sleep during a large portion of the recording sessions. Sleep stage was determined by simultaneously recorded EEG. Occasionally, chloral hydrate was used to induce sleep in anxious patients. In 2 patients (Cases 2 and 5) AEP recordings were also obtained during pentobarbitone sodium (Pentothal) anaesthesia immediately before temporal lobectomy in order to study the effect of barbiturates on AEPs.

The subdural electrode array was made up of either 16 or 32 3.1 mm stainless steel discs spaced 1 cm apart in a rectangular array and embedded in a silicone rubber plate (Lueders *et al.*, 1982). Steel wires connected to these discs were led out by way of a Teflon-insulated cable through an opening in the dura, skull and scalp fascia.

The reference electrode consisted of a silver chloride cup electrode applied to the fifth cervical spinous process with collodion. A subdural electrode distant from Heschl's gyrus was sometimes used as a reference when there was excessive neck muscle activity.

Cortical evoked potentials recorded from 16 subdural electrodes, including one channel linking the reference to ipsilateral hand, were simultaneously amplified and filtered (30 to 250 Hz, 6 dB down). A signal averager was used to analyse electrical activity during the first 40 ms after stimulus onset at a dwell time of 40 to 160 μs. Each trial consisted of 1000 samples, and 2 to 4 trials were obtained for each study. The results were printed out by a X-Y plotter. Sampling was discontinued whenever muscle activity was visible on the monitoring oscilloscope.

Polarity nomenclature employed is such that a positive potential recorded at the subdural electrode (relative to the reference) would be represented by a downward displacement, and upward for a negative potential.

The stimuli consisted of alternating condensation and rarefaction clicks of 100 μs duration presented through shielded headphones at 65 dB above the hearing threshold (65 dB sound level (SL)) to the ear contralateral to the subdural electrode array. When AEP recordings were made in the operating room, the click stimuli were delivered through earphones coupled by hollow tubes to both ears. This system produced a delay of about 0.5 to 1.0 ms in the peak latencies of the AEPs. A click rate of 6.8 Hz was used in all the studies except when we studied the effect of stimulus rate on AEPs. The unstimulated ear was masked with 40 dB (SL) white noise during monaural stimulations.

The effect of stimulus intensity on AEPs was studied in Case 2. Clicks at 6.8 Hz of varying intensities were presented to the contralateral ear and the corresponding amplitudes and latencies of the AEPs recorded from the subdural electrode registering the largest potentials were analysed as a function of intensity.

In addition, the effect of stimulus rate on AEPs was also studied in Cases 2 and 4. Continuous 65 dB SL clicks at varying rates were presented binaurally and the corresponding AEP amplitudes from the subdural electrode with the highest amplitude potentials were plotted as a function of the stimulus rate.

While contralateral monaural stimulation was employed in all patients, in 3 subjects (Cases 1, 2 and 4), we had the opportunity to use, in addition, ipsilateral monaural and binaural stimulation. The resulting effect on AEP amplitudes, latencies and topography was analysed.

Isopotential maps of individual AEP components to contralateral monaural stimulation were obtained on all patients. In Cases 1 and 2, corresponding maps for ipsilateral monaural and binaural stimulation were also plotted. The magnitude of each AEP component is represented by the peak-to-peak amplitude, defined here as the vertical distance from the preceding peak to the peak of the component under study. For the first cortical component (P1), the amplitude is measured relative to the immediately preceding peak which is unlabelled in this study. The average amplitude of each component recorded at an electrode was computed from 2 to 4 different trials. A similar process was repeated for AEPs at each of the remaining electrodes. Only well-defined and reproducible AEPs were used in constructing these isopotential maps. The average amplitude of each AEP component was then expressed as a percentage of the largest reponse obtained. Electrodes registering components with amplitudes of 80 per cent and above were represented by solid black circles. Amplitudes that are 60 to 79 and 50 to 59 per cent maximum were contained within consecutive concentric circles labelled '60' and '50', respectively. Activity less than 50 per cent of the maximum was excluded on the maps. An electrode recording activity with amplitude in excess of 50 per cent of the surrounding activity would be represented by a solid black circle enclosed within two concentric circles.

RESULTS

AEP Morphology

The typical AEP waveform recorded at the subdural electrode with the highest amplitude potentials consisted of a small positive peak PB (Positivity from the Brainstem) occurring at about 6 ms, followed by prominent positive-negative-positive peaks with average latencies of 15.8 ± 0.2, 21.2 ± 0.2 and 28.8 ± 0.3 ms,

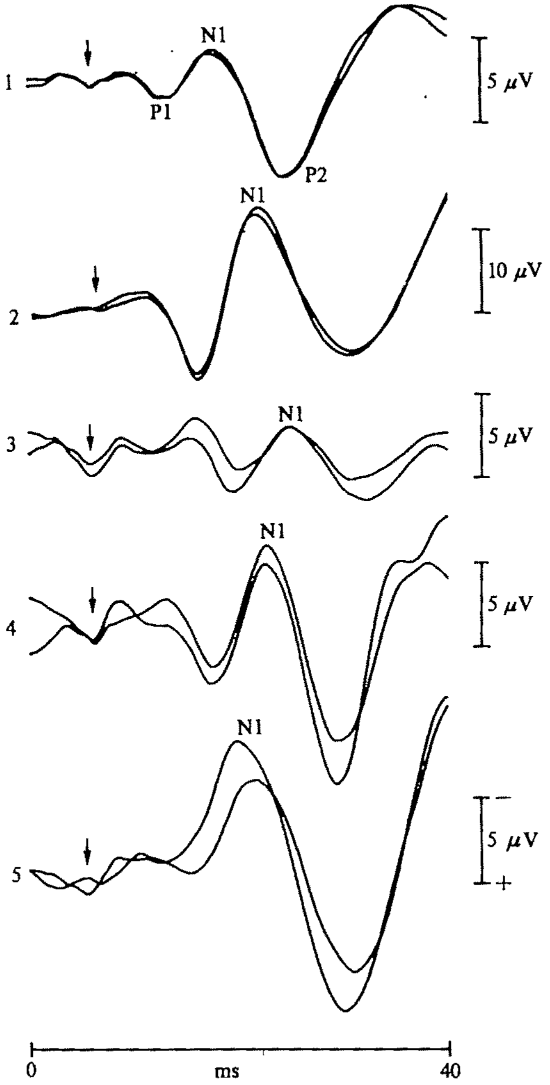

FIG. 1. Representative cortical AEPs to contralateral monaural stimulation in the 5 subjects. They were recorded at the subdural electrode with the highest amplitude potentials and referenced to the fifth cervical spinous process. Each tracing is the average of 1000 responses and the tracings from two separate trials are superimposed for each patient. The nomenclature proposed by Celesia *et al.* (1968) is adopted here. The exception is component PB, which represents the brainstem component recorded when a neck reference is used. PB is labelled with an arrow in this figure.

respectively (fig. 1). These latter components were labelled P1, N1 and P2, after the nomenclature proposed by Celesia *et al.* (1968) for primary AEPs. Component PB is in effect peak V of the auditory brainstem potentials and was seen only when the cervical spine reference was used. Substitution of this reference with a subdural electrode distant from Heschl's gyrus resulted in cancellation of this component, thus attesting to its far-field origin. The individual brainstem components can actually be resolved by widening the filter setting to 150–1500 Hz. Since PB is not a cortical component, it will be excluded from the following discussion of cortical AEPs.

Components P1, N1 and P2 were seen consistently in all 5 patients (fig. 1) and had amplitudes ranging from 0.5 to 7.5 μV with contralateral monaural stimulation. The largest component was usually P2, followed by N1 and then P1. Exceptionally large AEPs, almost ranging from 3 to 6 times the size of the others, were recorded from Case 2. The peak latencies and amplitudes of P1, N1 and P2 for the 5 patients are displayed in the Table. The intertrial variability of AEP peak latencies at the electrode with the highest amplitude potentials was relatively small, usually no more than 0.8 ms. In contrast, the intertrial amplitude variation was quite significant, ranging from 0.1 to 2.5 μV. Despite these variations, the cortical AEPs maintained consistent waveforms that were relatively reproducible from trial to trial in the same patient.

TABLE. AEP PEAK LATENCY AND AMPLITUDE TO CONTRALATERAL MONAURAL STIMULATION

	P1		*N1*		*P2*	
Case	*Latency (ms)*	*Amplit. (μV)*	*Latency (ms)*	*Amplit. (μV)*	*Latency (ms)*	*Amplit. (μV)*
1	12.7 ± 0.1	1.5 ± 0.0	17.4 ± 0.1	3.1 ± 0.2	24.2 ± 0.1	7.5 ± 0.1
2	15.4 ± 0.1	8.3 ± 0.2	21.2 ± 0.0	17.1 ± 0.3	30.3 ± 0.1	15.0 ± 0.4
3	19.4 ± 0.1	1.6 ± 0.1	24.4 ± 0.0	1.6 ± 0.2	31.2 ± 0.3	1.9 ± 0.2
4	17.5 ± 0.2	2.0 ± 0.1	22.1 ± 0.1	3.0 ± 0.6	29.1 ± 0.1	6.0 ± 0.5
5	14.1 ± 0.5	0.5 ± 0.2	20.2 ± 0.6	2.5 ± 0.4	29.1 ± 0.8	5.7 ± 0.8

The recordings were obtained from the subdural electrode with the highest amplitude potentials in each of the 5 subjects, averaging 1000 responses. The reference electrode was located at the fifth cervical spinous process. The values were computed from three to four trials each and the corresponding standard error is shown.

While the major proportion of the AEP recordings was obtained with a neck reference, in a few it was necessary to replace it with a subdural electrode distant from Heschl's gyrus on account of excessive neck muscle activity. This reference change usually had no effect on P1, N1 and P2 peak latencies, but in some cases resulted in higher AEP amplitude (up to 63 per cent). This is most likely due to an increase in signal noise ratio resulting from a reduction in muscle activity. With this montage, the brainstem component PB is cancelled owing to its far-field origin.

AEP Distribution

A representative AEP recording generated by binaural stimulation from Case 2 is shown in fig. 2. It is readily apparent that electrode 7 in the suprasylvian region near the motor cortex recorded the largest AEPs. Electrodes superior and proximal to it also displayed AEPs with relatively similar morphology but of much lower amplitude (less than 50 per cent). In this case, components P1, N1 and P2 all had the highest amplitudes at the same electrode. However, in 2 patients (Cases 4 and 5), these components had different distributions, although the largest potentials were recorded consistently at one and the same electrode on the superior temporal gyrus. A variation from this pattern is evident in Cases 1 and 3. In both instances, components P1 and N1 had maximum amplitudes in two adjacent electrodes. The former case is illustrated in fig. 6A.

The locations of the subdural electrode with the highest amplitude potentials as determined by contralateral monaural stimulation for the 5 patients are represented by circles with the corresponding patient's identification number in fig. 3. In instances where the patient had two subdural electrodes registering the highest amplitude potentials, the midpoint between these two electrodes was selected to represent the area of maximal activity. These electrodes were on the superior

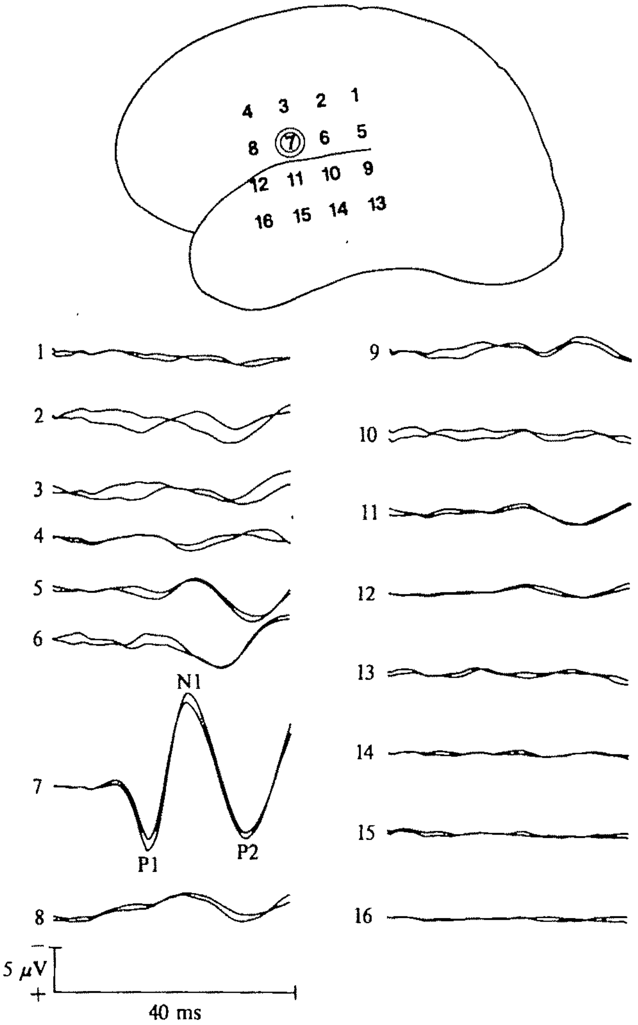

FIG. 2. Cortical AEP distribution in *Case 2.* The numbers next to each tracing correspond to the subdural electrode position on the brain. The AEPs were generated by binaural stimulation and each tracing is the average of 1000 responses. AEPs from two separate trials were superimposed at each electrode. The reference consisted of a subdural electrode distant from Heschl's gyrus.

temporal gyrus (1 cm from the sylvian fissure) in 3 patients (Cases 3, 4 and 5) and in the suprasylvian region near the motor cortex (1 cm from the sylvian fissure) in 2 patients (Cases 1 and 2). The average distance of these electrodes from the temporal tip was 59 mm, with a range of 50 to 65 mm. Intraoperative measurements were accurate to about 5 mm.

Effect of Ipsilateral Monaural and Binaural Stimulation

In Cases 2 and 4, the behaviour of AEPs at the electrodes with the highest amplitude potentials to ipsilateral monaural and binaural stimulation were investigated. Only the data for Case 4 will be presented. The peak latencies of cortical AEPs did not change as a function of the ear stimulated, although at times,

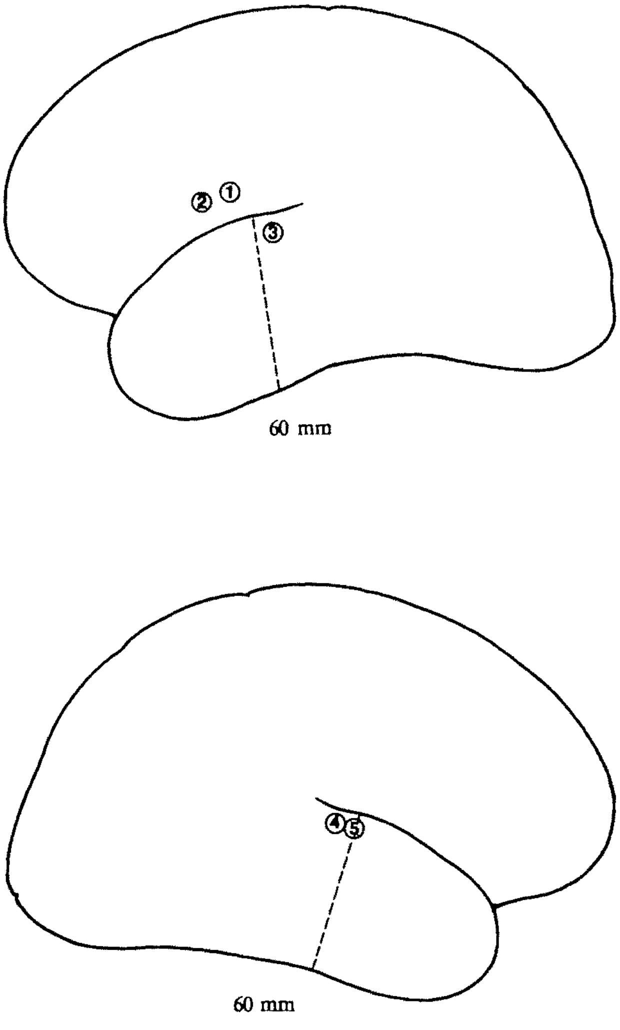

FIG. 3. Location of the subdural electrodes with the highest amplitude potentials as determined by contralateral monaural stimulation in the 5 subjects. Averages of 1000 responses were used and the reference electrode was located at the fifth cervical spinous process. Electrodes 1, 2, 3, 4 and 5 correspond to Cases 1, 2, 3, 4 and 5, respectively. The 60 mm mark refers to the distance from the tip of the temporal lobe.

apparently random latency shifts of 0.3 to 2.6 ms were observed (fig. 4). On the other hand, the side of stimulation had a significant effect on AEP amplitudes. The amplitudes of P1, N1 and P2 were largest with binaural stimulation, intermediate with contralateral monaural and smallest with ipsilateral monaural stimulation (fig. 4). The graph on fig. 5 shows AEP amplitude expressed as a percentage of the amplitude obtained with binaural stimulation on the y-axis, and the side of stimulation on the x-axis for Case 4. The amplitudes of the individual components were 70–80 per cent of maximum with contralateral monaural stimulation, and 40 per cent maximum with ipsilateral monaural stimulation.

The effect of the side of stimulation on cortical AEP topography was studied in detail in Case 1. Fig. 6 shows that the isopotential maps for components P1, N1 and P2 were relatively constant for both monaural and binaural stimulation. The electrodes with the highest amplitude potentials shifted less than 1 cm from one condition to another.

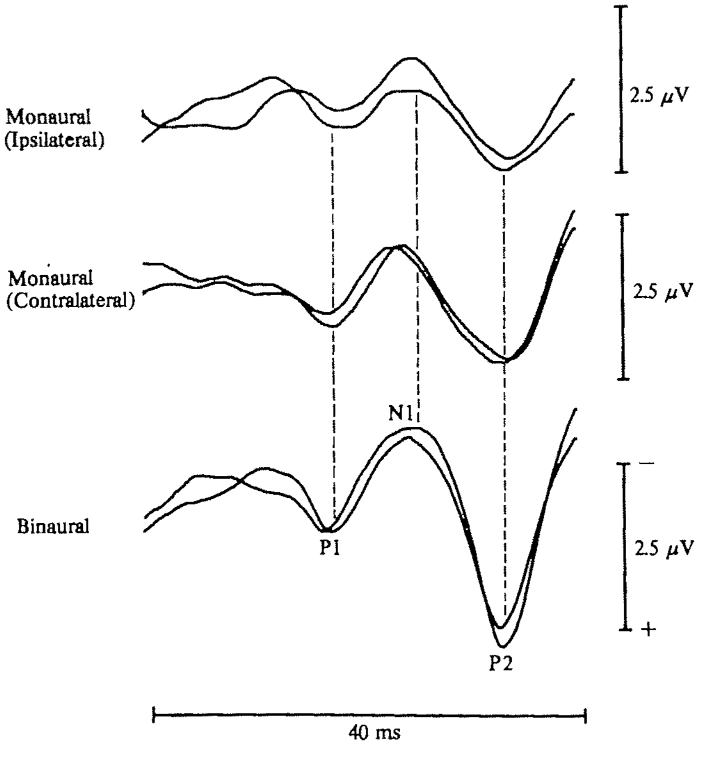

FIG. 4. Effect of monaural (ipsilateral and contralateral ear) and binaural stimulation on the cortical AEPs in *Case 4*. These potentials were recorded from the subdural electrode with the highest amplitude potentials and the tracings from two separate trials are superimposed. Each tracing is the average of 1000 responses. A subdural electrode distant from Heschl's gyri was used as the reference in these recordings.

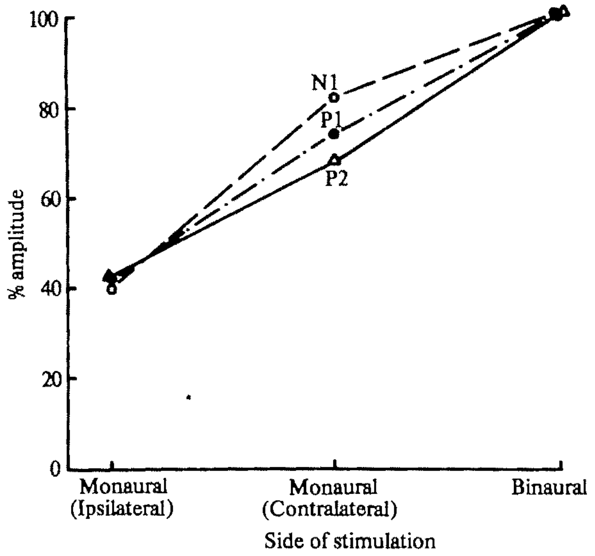

FIG. 5. Effect of monaural (ipsilateral and contralateral ear) and binaural stimulation on cortical AEPs in *Case 4*. The side of stimulation is indicated on the x-axis. The AEP amplitude expressed as a percentage of the amplitude obtained with binaural stimulation is represented on the y-axis. Conditions of recording as in fig. 4.

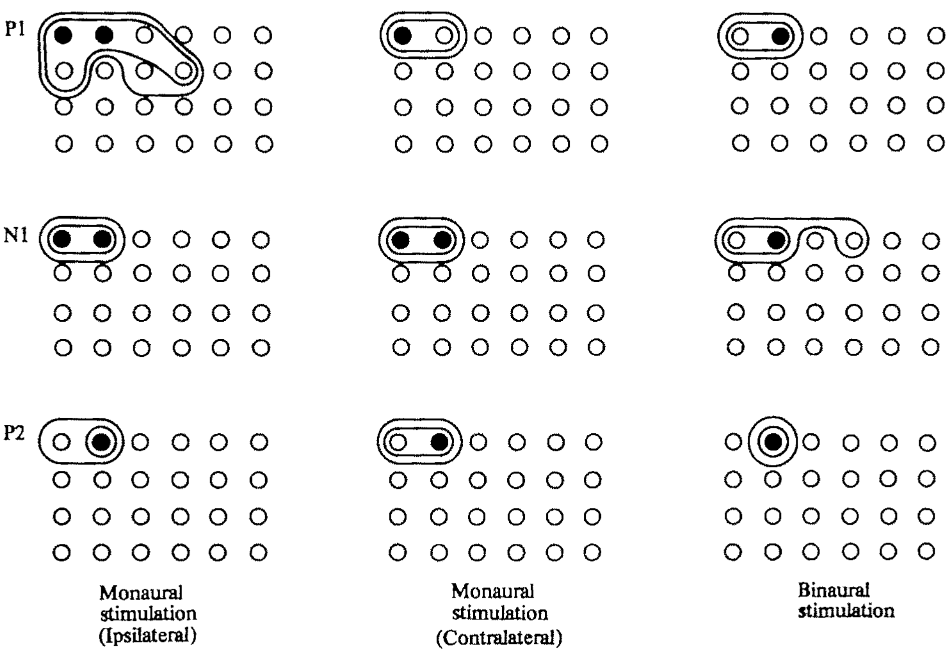
P1
N1
P2
Monaural stimulation (Ipsilateral)
Monaural stimulation (Contralateral)
Binaural stimulation

FIG. 6. Cortical AEP distribution evoked by monaural (ipsilateral and contralateral ear) and binaural stimulation in *Case 1*. Conditions of recording as in fig. 4. Isopotential maps for each of the AEP components are shown. The electrodes with the highest amplitude potentials are coloured black. Electrodes encircled by the '60' and '50' contour lines recorded AEPs with amplitudes 60 to 79 per cent and 50 to 59 per cent, respectively, of the highest amplitude potentials.

Effect of Stimulus Rate

The effect of stimulus rate on AEP amplitude was studied in Cases 2 and 4, but only the data from the latter patient will be presented, since in this case the AEPs were unusually large and well-defined, even at fast stimulation rates (fig. 7). A period of relative unresponsiveness below 10.1 Hz is evident for components N1 and P2. Components P1 and P2 were not analysed below 20 and 10.1 Hz, respectively, because they could not be identified with confidence at the faster stimulation rates (fig. 8). Note that at a click rate of 40.1 Hz, a frequency following response was elicited and only component N1 could be clearly identified. Relatively full recovery occurred after 10.1 Hz for components P1 and N1, and after 2.5 Hz for P2. The latter component displayed a period of 'supernormality' between stimulus rate of 10.1 and 2.5 Hz.

Effect of Stimulus Intensity

The effect of stimulus intensity on AEP amplitude was investigated in Case 2 (fig. 9). AEPs became identifiable at 0 dB sound level (SL), that is, when the patient first reported hearing the clicks. The amplitude of all components then increased somewhat linearly with rise in intensity until about 25 dB SL. At this point, components P1 and N1 (and also P2 to a lesser degree) broke the pattern by forming a brief plateau before resuming their ascent, but this time, at a slower rate.

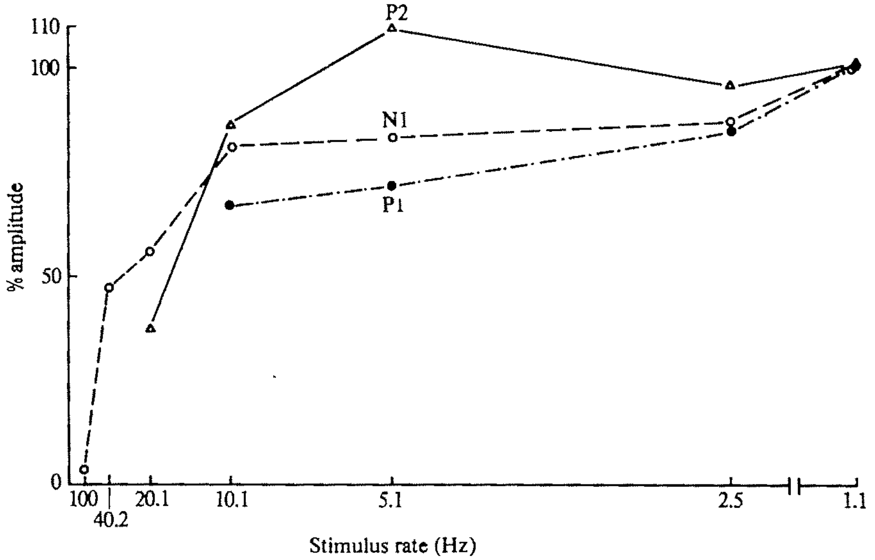

FIG. 7. Effect of stimulus rate on AEPs evoked by binaural stimulation in *Case 2*. The stimulus rate (in Hz) is represented on the x-axis. AEP amplitudes expressed as a percentage of the amplitude at stimulus rate of 1.1 Hz are represented on the y-axis. AEPs recorded at the subdural electrode with the highest amplitude potentials were used. Averages of 1000 responses were employed and the reference electrode was located at Cz.

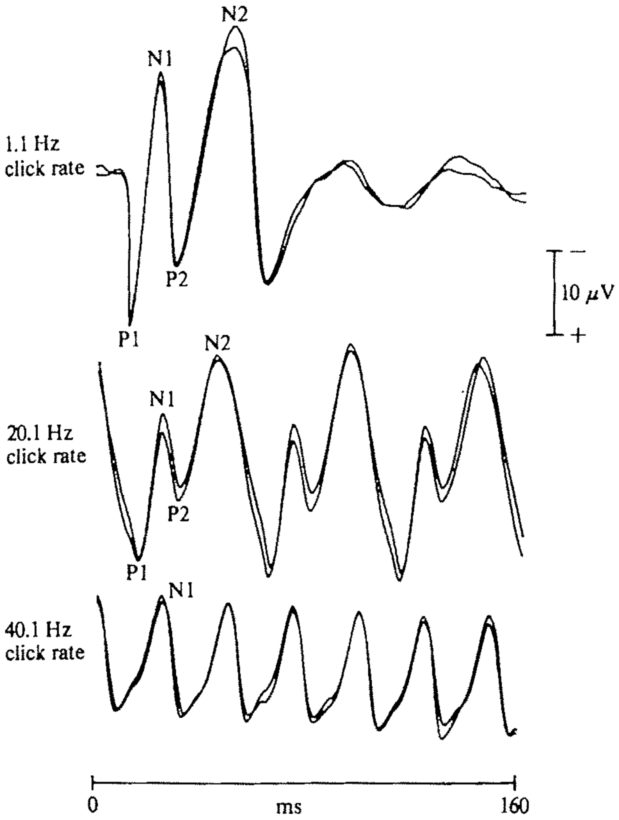

FIG. 8. Effect of stimulus rate on AEP morphology in *Case 2*. Conditions of recording as in fig. 7. The nomenclature proposed by Celesia *et al.* (1968) is adopted here.

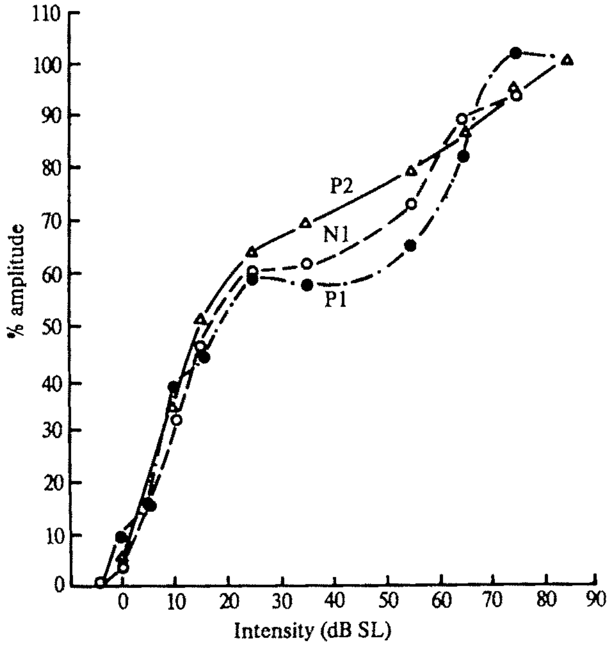

FIG. 9. Effect of stimulus intensity on AEP amplitude in *Case 2*. The stimulus intensity in dB SL is represented on the x-axis, while the AEP amplitude expressed as a percentage of the amplitude evoked by 85 dB SL clicks is shown on the y-axis. AEPs recorded from the subdural electrode with the highest amplitude potentials to contralateral monaural stimulation were used. Averages of 1000 responses were employed and the reference consisted of a subdural electrode distant from Heschl's gyri.

The peak latency-intensity function was also analysed in the same patient. All components showed a drop in peak latency with increase in stimulus intensity. This decrease in latency was 2.5 ms for P1, 2.0 ms for N1 and 1.5 ms for P2 between 5 and 85 dB SL. The decrease in latency was approximately a linear function of stimulus intensity.

Effect on Barbiturate Anaesthesia

AEP recordings were obtained in Cases 2 and 4 15 to 30 min after the injection of 450 mg (6.0 mg/kg) of pentobarbitone sodium (Pentothal). The injection was given intravenously as a bolus. The results were similar in both subjects. In Case 2, a 26 to 48 per cent drop in AEP amplitude and an associated peak latency shift of between 0.7 to 2 ms were observed (fig. 10). The AEPs maintained their morphologies even when recorded about 15 min after the initiation of nitrous oxide general anaesthesia.

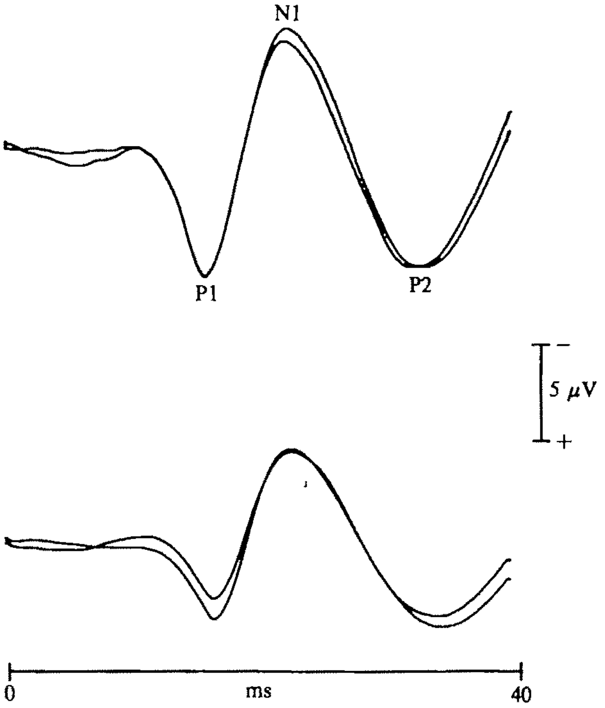

FIG. 10. Effect of pentobarbitone sodium (Pentothal) anaesthesia on the cortical AEPs in *Case 2*. The AEPs were evoked by binaural stimulation and recorded from the subdural electrode with the highest amplitude potentials. Averages of 1000 responses were employed and the reference consisted of a subdural electrode distant from Heschl's gyri. The recordings were obtained before (*upper traces*) and 15 to 30 min after the intravenous injection of 450 mg of Pentothal (6.0 mg/kg) (*lower traces*).

DISCUSSION

Celesia and Puletti (1969) recorded AEPs from Heschl's gyri and from the cortical surface in an area including the posterior two-thirds of the superior temporal gyrus, the frontal and parietal opercula. The potentials from the lateral cortical surface were described as being relatively small and labile. They speculated that these AEPs could either be volume-conducted from the primary auditory cortex, or were generated locally from the equivalent of auditory association or polysensory areas in animals. The former hypothesis was thought unlikely because the AEP waveforms were different and peak latencies were longer than those of the primary AEPs in Heschl's gyri, and also because they were sensitive to anaesthesia.

The AEPs recorded by us with subdural electrodes, however, were similar to the early cortical components recorded directly from Heschl's gyri by Celesia and Puletti (1969). In using somewhat different recording parameters, such as a narrower filter (30 to 250 Hz instead of 1 to 3000 Hz), a faster click rate (6.8 Hz instead of 1 Hz) and a larger sample size (1000 instead of 50), we were able to record relatively stable and reproducible responses from the posterior perisylvian region. These AEPs generally had highest amplitudes at 1 or 2 electrodes and a relatively steep potential gradient at adjacent electrodes. The AEP morphology was similar in all 5 patients and identical to primary AEPs recorded by Celesia and Puletti (1969). The peak latencies of the AEP components fell within the range quoted for the primary AEP recorded from Heschl's gyri in man (Celesia, 1976), although their amplitudes were at least six times smaller (amplitudes of AEPs generated by binaural stimulation used for the comparison).

The subdural electrodes with the highest amplitude potentials were located on the banks of the sylvian fissure at an average distance of 59 mm from the temporal tip. They were all in the vicinity of Heschl's gyri whose lateral borders extend from 35 to 70 mm relative to the temporal tip (Celesia and Puletti, 1969), and in close proximity to the region on the supratemporal plane from which primary AEPs have been recorded. This latter area is located 56 to 69 mm, and in one patient, as close as 50 mm from the temporal tip (Celesia and Puletti, 1969). (It is important to note the limitations of a fixed electrode array for localization purposes. Owing to the nature of its construction, the electrode with the highest amplitude potentials could conceivably reflect activity generated anywhere in a 3.1 mm radius rather than from immediate underlying cortex. Thus, an error of 3.1 mm is inherent with this method of localization.)

The above findings are strongly supportive of a near-field origin for the subdurally recorded AEPs, that is, these AEPs are volume-conducted from the immediately adjacent primary auditory cortex within the sylvian fissure. The relatively lower amplitudes and less steep potential gradients of our AEPs are consistent with this hypothesis. The potential field gradient of the primary AEP in the macaque monkey is known to have a very steep gradient, such that a significant drop in potential is seen as one moves short distances away from the generator

(Arezzo *et al.*, 1975). The same holds true for human somatosensory evoked potentials which are produced by surface generators and therefore can be recorded quite easily. Using chronic subdural electrodes, we have found somatosensory evoked potentials to be extremely focal in distribution, such that they would be attenuated up to twelve times if recorded 1 cm away from the electrode with the highest amplitude potentials (Lueders *et al.*, 1983). Drawing the same analogy, it is therefore not surprising that our subdural electrodes, which in all but one case were distal to the primary AEP generator within the fissure, recorded AEPs similar in morphology to the primary AEPs but had smaller amplitudes and relatively less steep potential gradients.

The location of the electrodes with the highest amplitude potentials on the superior temporal gyrus in 3 patients, and the suprasylvian region near the motor cortex in 2 patients, can perhaps be explained by the orientation of the AEP dipole generator, being tilted at an acute angle to the superior temporal plane in the former cases and obliquely in the latter. An alternative explanation for the suprasylvian location of these electrodes (Cases 1 and 2) would be that the AEPs are locally generated. This would be in good agreement with the recent anatomical study of Galaburda and Sanides (1980) who found auditory-related cortex in the parietal operculum and inferior parietal lobule in man.

Celesia *et al.* (1968) also described long latency AEPs from the precentral region that they felt were of local origin because they persisted after the removal of Heschl's gyrus. Cases 1 and 2 had electrodes with the highest amplitude potentials in this area, but the peak latencies of the recorded AEPs were within the range for primary AEPs and not delayed as in the case reported by Celesia *et al.* (1968). Thus, it is likely that the recorded AEPs in these patients were either volume-conducted from Heschl's gyrus or locally generated in the suprasylvian auditory cortex.

In Case 2, the electrode with the highest amplitude potentials was suprasylvian in location and the recorded AEPs were unusually large compared with the other patients and had steep potential gradients comparable to that produced by surface generators. The latter finding suggests that the electrode is directly over the primary auditory cortex. The aforementioned report of Galaburda and Sanides (1980) clearly supports this possibility. Primary AEPs have also been recorded on the banks of the sylvian fissure in monkeys which have a somewhat similar anatomical arrangement of the primary auditory cortex as humans (Pribram *et al.*, 1954). That the amplitude of this AEP is still below the range quoted for the primary AEP in man (Celesia and Puletti, 1969) may be due to the fact that only a portion of the electrode surface was in contact with the primary auditory cortex.

Our findings on the effect of the side of stimulation on the AEPs are in agreement with the data reported for primary AEPs in both man (Celesia, 1976) and cats (Rosenzweig, 1951). The AEP amplitudes were largest with binaural, intermediate with contralateral monaural and smallest with ipsilateral monaural stimulation. From this data, it is clear that there is a significant representation of the ipsilateral ear on the primary auditory cortex, although the contribution of the contralateral ear is usually larger. That the sum of the amplitudes of the components to ipsilateral and contralateral monaural stimulation is always larger than the amplitude of similar components to binaural stimulation suggests that there is overlap between the neuronal populations activated by ipsilateral and contralateral monaural stimulation. That the AEP peak latencies were not significantly affected by the side of stimulus presentation would suggest that the conduction times for ipsilateral and contralateral auditory pathways are relatively similar, and that transcallosal pathways are not used to any significant degree in the generation of the early cortical AEPs to contralateral or ipsilateral stimuli.

The effect of stimulus rate on AEP amplitude showed cyclic changes very similar to those of the primary auditory cortex of mammals (Tunturi, 1946; Borsanyi, 1964) and in man (Celesia, 1976). Compared with Celesia's study (1976), however, we observed a less significant depression with fast stimulus rates. N1, for example, was only reduced to half its amplitude at a stimulus rate of 40.2 Hz, whereas Celesia (1976) did not record any response at that stimulus rate. In addition, the period of facilitation described by Celesia (1976) for stimulus rate between 4.0 to 5.0 Hz (interstimulus interval of 200 to 250 ms) was less clearly defined and only evident for P2 in our studies. These relatively minor differences could be due to interindividual variability, reported as very high for recovery curve studies of evoked potentials (Lueders *et al.*, 1984), or due to differences of methodology (paired clicks of stimuli *vs* continuous clicks).

The intensity curve is remarkable in that the AEPs became detectable at the same time that the patient was able to hear the click stimuli. This would imply that the perception of even elementary auditory stimuli requires the activation and participation of primary cortical mechanisms. The intensity curve is essentially 'triphasic' for P2, showing a brief interval between 25 to 55 dB SL where an increase in intensity is associated with no or only minimal increase in AEP amplitudes. This curve is similar to the one obtained for the primary AEP in cats by Teas and Kiang (1964). It is interesting to note, however, that the intensity curve for brainstem component V is clearly different in that it lacks the plateau in the middle intensity range. This suggests that the aforementioned 'triphasic' curve is an expression of synaptic processing of the afferent signal above brainstem level. The inverse relationship between AEP peak latencies and stimulus intensity seems to be a property common to both cortical and brainstem potentials (Stockard *et al.*, 1979).

Prolongation of the peak latency and attenuation of the amplitude of the primary AEP have been reported in man under halothane and nitrous oxide anaesthesia (Celesia and Puletti, 1971). Similar effects were seen in the AEPs recorded from Cases 2 and 5 during Pentothal induction with the exception that the peak latencies were only minimally delayed. This difference may be explained by the different anaesthetic agents used in the two instances. The above effects have also been reported for the primary AEP in cats (Pradhan and Galambos, 1963). The relative resistance of the early AEPs recorded with subdural electrodes to barbiturates supports our conclusion that we are dealing with primary sensory potentials (Goff *et al.*, 1977).

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PERCEPTION OF BODY WEIGHT AND BODY MASS AT TWICE EARTH-GRAVITY ACCELERATION LEVELS

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SUMMARY

1. On Earth, when standing on two feet, we experience particular patterns of force and pressure on the soles of our feet. As we lift one foot and balance on the other, little or no increase in force or pressure is perceived on the sole of the stance foot even though the contact forces of support on that foot have doubled. The failure to perceive this increase is actually an illusion resulting from the operation of spatial constancy mechanisms serving to preserve feelings of near constant force and pressure on the support surface(s) of the body.

2. On Earth, body weight and body mass are perceived as remaining constant regardless as to whether we are standing on two feet or one and whether we are carrying large objects. In the high force phase ($2\,g$ acceleration) of parabolic flight, body weight is perceived as doubling, and a great increase in force is perceived on the soles of our feet if we are standing. When shifting balance from two feet to one, an increase in force of approximately $0.5\,mg$ is felt on the sole of the stance foot. The actual increase in force is $1.0\,mg$ but perceptual compensation is only being made for a $0.5\,mg$ increase such as would be characteristic of shifting balance on Earth; accordingly an additional $0.5\,mg$ ($1.0-0.5\,mg$) residue is perceived. These findings indicate that body weight is dependent on the magnitude of the gravitoinertial forces acting on the body. Variations in the contact forces supporting the body due to passive or active locomotion of the body or to objects that are being carried are monitored and disregarded in computing apparent body weight.

3. When stepping up and down from a low platform during the high force phases of parabolic flight, aberrant motion of the body and the aircraft is experienced. These illusory motions result because the doubling of body weight in a $2\,g$ force background alters the normal relationship between patterns of α and γ activation of antigravity muscles, muscle spindle activity, and the movements of the body. Accordingly, sensory-motor control and perceptual and postural stability on Earth are dependent on an active calibration to a $1\,g$ background force level.

INTRODUCTION

We describe here the misperceptions of the forces acting on the human body that occur during body movement in the increased gravitoinertial force phases of parabolic flight. The significance of these observations will be shown to lie in their implications for the perception of body weight and body mass under normal terrestrial conditions. They demonstrate that perception of weight and of the forces acting on the body is 'calibrated' in relation to the contact force patterns characteristic of movement and sūpport of body mass under Earth gravity acceleration levels. When the magnitude of the background acceleration acting on the body is altered significantly, a variety of postural illusions, illusions of substrate motion, and illusions involving aberrant perception of force and pressure result because sensory-motor and postural control is actively adjusted to a standard background of a 1 g acceleration, and this standard is no longer appropriate.

The physical weight of a body on Earth is determined by the mass of the body, m, and the acceleration of gravity, g. It is notable, however, that the receptors which transduce the contact forces of support acting on and within the body cannot distinguish between forces opposing gravitational acceleration and those opposing inertial acceleration; instead, they respond to the resultant gravitointertial acceleration (*see* Patterson and Graybiel, 1974). Nevertheless, as we move about under terrestrial conditions, we experience a more or less constant apparent weight of our body even though in moving we apply forces to our body. That is, we do not experience the fluctuations in contact forces on our body as changes in perceived weight. For example, when hopping or running, there are great variations in the contact forces acting on our body, for example, from 0 to 2 mg. Despite these changes in force level, comparable changes in apparent body weight do not occur, nor do we experience comparable changes in the forces acting on our body. This latter point will be further illustrated later. It should be noted, too, that because our body weight does not seem to change when carrying objects, we necessarily 'correct' the contact forces of support for the contribution of such objects to the overall force levels. In fact, departures of the total contact forces of support from 'normal levels', coupled with information about the magnitude of muscle forces generated to support the object and to maintain balance, may be one aspect of the way we determine the weight of objects we are carrying.

On Earth, when standing, we experience a particular weight of our body and specific patterns of force and pressure on the soles of our feet. The forces on the feet arise from the surface of support which—when the body is stationary or moving at constant velocity—precisely counteracts the gravitational acceleration vector, g. In the absence of such contact forces of support, no pressure is felt on the surface of the body and the body feels weightless or free floating (Lackner and Graybiel, 1979, 1983). When standing, if we lift one of our legs and balance on the other, we experience no change in apparent body weight and the force or pressure on the sole of our support foot seems to change little, if at all. This situation is illustrated in fig. 1, panel A. The failure to perceive a great change in force on the sole of the support foot is actually an illusion because the contact force on its sole has increased twofold. Similarly, if while standing on both legs we rock forwards to balance on our toes or backwards to our heels, we experience no change in weight and little change in apparent pressure on the support area(s) of our body. Because the Weber fractions for detecting changes in hefted weight and in pressure are of the order of 0.05 and 0.15, respectively (Weber, 1978), the changes in force and pressure on the stance foot or feet are well above threshold. This can easily be demonstrated by varying the force and pressure on the soles of a recumbent individual's feet. Under those circumstances we have found that difference thresholds are at least as sensitive as the Weber fractions cited. Such observations which the reader can easily repeat indicate that the perception of body weight is determined on the basis of the total support forces acting on the body.

The absence of changes in apparent body weight during movement under terrestrial conditions means that we monitor our active and passive body motions and 'attribute' fluctuations in contact forces of support to motion of our body mass rather than to fluctuations in body weight. Moreover, as will be shown, the variations in magnitude of these contact forces are not perceived accurately but tend to be greatly underestimated. This underestimation reflects the operation of spatial constancy mechanisms providing ongoing information about the orientation of our body to the environment and assuring perceptual and postural stability (Lackner,

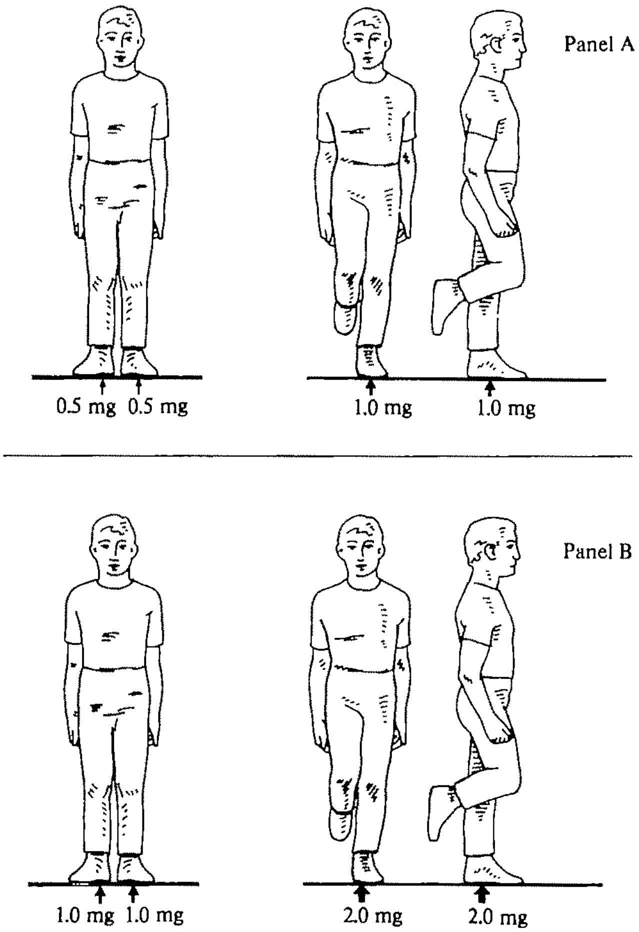


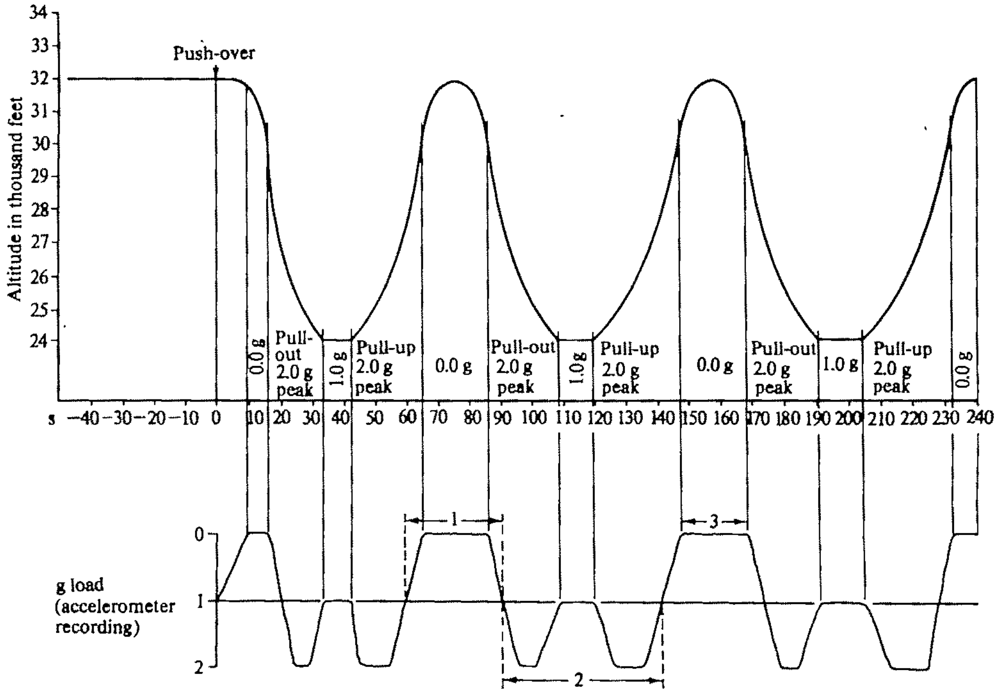
FIG. 1. Panel A shows the contact forces of support acting on the feet of a subject standing on Earth. Panel B shows the forces on the subject's feet when he is exposed to twice Earth-gravity acceleration levels. In the absence of a support substrate, the subject would be accelerated downwards.

1978, 1981). The operation of these mechanisms can be better appreciated by a consideration of the patterns of force, pressure and weight experienced during body movement in the increased gravitoinertial phases of parabolic flight.

METHODS

In our experiments, a modified Boeing KC-135 aircraft was flown through a series of Keplerian trajectories to create alternating periods of free fall ('0 *g*') and increased gravitoinertial force. The flight profile is illustrated schematically in fig. 2. The experiments to be described have been carried out with 6 normal observers with uniformly consistent results; informal observations have been made on 7 additional observers with the same results. Testing always began in the pull-up phase of a parabola, when the force level indicated by a digital accelerometer reached 1.8 *g*; the pull-out phase which is more variable was not used. This then allowed 15 to 20 s per parabola during which data could be collected (*see* fig. 2). The average peak force level in the parabolas in which data were collected was 1.88 *g*, range 1.82 to 1.97 *g*. There was no relationship between a particular flight and the force levels of the parabolas in that flight.

The 6 observers tested systematically ranged in age from 22 to 39 years, mean 28; all were male. Each of them had participated in earlier parabolic flight experiments and were experienced in moving about both in the high force and free fall phases of flight. A minimum of twenty-four weeks had elapsed since an individual's last parabolic flight sequence and his testing in the present experimental series.



1. Subgravity period. 2. Supragravity period: two high-force phases. 3. Weightless period.

FIG. 2. Schematic illustration of the flight profile of the Boeing KC-135 aircraft used in our experiments.

Two kinds of experimental observations were made by each subject. The first observations concerned body weight. The standing subject using magnitude estimation procedures (Stevens, 1957) was required to indicate the extent to which his apparent body weight (as experienced in straight and level flight) seemed to change on exposure to the high force phases of the parabolas. Each subject was aware of the distinction between mass and weight and had been instructed to judge the apparent heaviness or weight of his body. The weight experienced while standing on both feet in straight and level flight was used as the reference or standard and assigned the value 1. Accordingly, a weight twice as great would be given the rating 2, one half as great, 0.5. After judging body weight while standing on two feet, the subject balanced on his preferred foot and rated (1) how much he seemed to weigh, and (2) the extent to which the apparent force on the sole of his stance foot had changed in relation to the reference level. Each of these judgements was made at least 10 times by the subject over the course of the first several parabolas of the flight in which he was tested. Each subject was tested on a separate flight. None of the subjects had difficulty balancing on one foot during exposure to the high force levels because of their prior experience in standing and walking under such conditions.

The second set of observations (conducted on different flight days) concerned the patterns of force experienced when stepping up and down from a 15 cm high platform, 61 × 46 cm, bolted to the deck of the aircraft. These observations were undertaken both in straight-and-level flight (1 *g* gravitoinertial force level) and in the high-force pull-up phase of parabolas when the force level exceeded 1.8 *g*. The subject's task was to stand on two feet in front of the platform, then step up onto the platform with both feet. The subject then stepped back onto the aircraft deck and stood on two feet. Emphasis was placed on moving in a normal way at a normal pace. Each subject repeated this pattern at least 10 times in straight and level flight and in the high force phase of successive parabolas at the beginning of a flight. The subjects compared the apparent forces on the soles of their feet as they stepped up, stood on, and stepped off the platform to the 1 *g* stepping values. They also reported whether the aeroplane deck and the platform seemed stationary as they went through their stepping motions. If the platform did not seem to be stationary, the subjects reported its direction of apparent motion and rated its displacement in centimetres.

RESULTS AND INTERPRETATION

Perception of Force and Body Weight During Exposure to High Gravitoinertial Force Levels

During the increased gravitoinertial force (1.8 to 2.0 *g*) phase of flight, the contact forces of support acting on the body approximately double and observers report their weight as somewhat more than doubling. This increase in apparent body weight is not unexpected because when standing or seated the body is not in motion in relation to the aircraft and the increased force acting on the body is interpreted as an increase in body weight. In other words, as already mentioned above, in the static situation the subject cannot distinguish between gravitational forces and gravitoinertial forces and perceived weight is determined by the gravitoinertial acceleration and the mass of the body. With the acceleration doubled, apparent weight also increases because the contact forces of support on the body have doubled and the muscular effort required to maintain a stable standing or seated posture of the body has also increased.

When a subject is standing upright on both feet and then shifts his support entirely to one foot, no change in apparent weight is perceived (nor would one be expected); however, a considerable increase in force on the sole of the stance foot is felt. This increase in apparent force, although substantial, is not equivalent to a doubling of the force on the stance foot; instead subjects perceive that force as increasing by approximately 50 to 60 per cent. In other words, compensation in determining apparent force is still taking place as under normal terrestrial conditions but the standard being employed is a terrestrial standard. The effect of maintaining this standard is to disregard a 0.5 mg increase in force on the stance foot when shifting from two feet to one. In the 2 g phase of parabolic flight, when the subject switches from two feet to one the actual increase in force on the stance foot is 1 mg. Compensation is only being allowed for 0.5 mg and accordingly the subject perceives a 0.5 mg (1 $mg - 0.5$ mg) increase in force on the stance foot. *See* fig. 1 and Table 1. With continued exposure, we expect that subjects would progressively experience the increase in force on the sole of their stance foot to diminish until little, if any increase was experienced (*see* Lackner and Graybiel, 1982).

TABLE 1. ACTUAL AND PERCEIVED BODY WEIGHT AND FOOT CONTACT FORCE DURING EXPOSURE TO 1 AND 2 g GRAVITOINERTIAL ACCELERATION

	1 g acceleration level			*2 g acceleration level*		
	Standing on one foot		*Standing on both feet*	*Standing on one foot*		*Standing on both feet*
Weight						
Actual	1 mg	↔	1 mg	2 mg	↔	2 mg
Perceived	1.06 (± 0.07)		1.0	2.4 (± 0.23)		2.3 (± 0.21)
		n.s.			n.s.	
Force/foot						
Actual	1 mg	↔	0.5 mg	2 mg	↔	1 mg
Perceived	1.1 (± 0.09)		1.0	2.8 (± 0.25)		2.2 (± 0.19)
		n.s.			$P < 0.001$	

n.s. = $P > 0.05$.

Subjects using magnitude estimation rated their apparent body weight and the intensity of the contact forces on their feet while standing on one and on both feet during exposure to 1 g and to 2 g gravitoinertial acceleration levels. The apparent weight of the body experienced when standing on both feet in a 1 g acceleration field during straight and level flight served as the standard and was assigned the value 1. The apparent contact force on the feet while standing on both feet in straight and level flight served as the standard for judging contact forces on the feet and was also given the value 1. Means and standard deviations of estimates are presented. Significance levels were assessed with correlated one tailed t-tests, n = 6.

Stepping Up and Down from a Low Platform in Straight and Level Flight and in the High Gravitoinertial Force Phase of Parabolic Flight

When a subject is standing on both feet and then steps up onto the 15.2 cm high platform during straight and level flight, a significant force increase on the sole of the support foot is noticed when the other leg is raised and moved forwards. As he then steps onto the platform shifting weight to the stepping leg and extending it to raise the body onto the platform, a shift of weight to the stepping foot is experienced—a weight shift corresponding to the normal apparent weight of the body. This is true even though there is momentarily an increase in force on the sole of the stepping foot above 1 *mg* and considerable work is being done in raising the centre of mass of the body. Subjects are not aware of this force fluctuation. When the other foot is brought into contact with the platform and support is distributed equally across the two feet, neither a change in apparent body weight nor in the forces on the feet is perceived. It should be noted that when stepping onto the platform the platform is correctly perceived as being stationary. All the motion experienced by the subject is motion of his body in relation to the aircraft and platform.

When stepping off the platform, a shift of weight to the stepping foot is experienced; a large increase in force on the stepping foot, relative to stance levels, is not experienced even though in lowering the centre of mass of the body rapidly, the force level may rise well above 1.5 *mg*. This dramatic increase in contact force on the stepping foot is shown in fig. 3 which is a force record of a subject stepping off the 15 cm high platform. When stepping down is completed with lowering of the other foot and support is distributed across the two feet, the 'normal' pattern of forces on the feet and of apparent body weight is experienced. During stepping down, the platform and the floor are perceived as remaining stationary throughout.

A very different pattern is experienced by subjects in stepping up and down from the same platform during exposure to increased levels of gravitoinertial force (1.8 to 2.0 *g*). As already described, the subjects experience doubling of body weight, and in raising one foot a great increase in apparent force on the stance foot; but when beginning to step up and shifting weight to the stepping foot, a much greater than normal effort is experienced and required in raising the body. This sense of great effort is coupled with the compelling feeling that the platform moves downwards 5 or 6 cm as stepped onto (*see* Table 2). Once weight transfer to the stepping foot is complete, the platform is perceived as stationary. A decrease in force on the sole of the stepping foot is felt when the other foot is brought into a position of support.

When stepping down from the platform an abnormally hard 'landing' is experienced, much as when descending a flight of stairs and overestimating the number of steps. Coupled with the sensation of too hard a landing is the feeling that the deck has risen upwards 4 to 8 cm to meet the stepping foot. After weight transfer

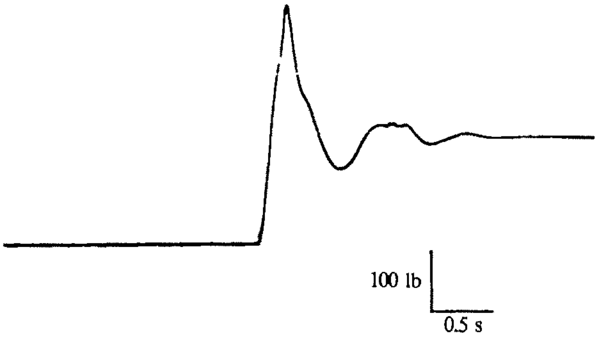


FIG. 3. Force record of a subject stepping down rapidly from a 15 cm high platform. The first upward deflection resulted when the subject's leading foot made contact, the second upward deflection occurred when the other foot was brought into place. Force changes were measured with a Kistler biomedical platform and displayed on a storage oscilloscope for photographing. Note that the peak force attained on the stepping foot is nearly 400 lb. The subject's weight was approximately 175 lb.

to the stepping foot is complete and lowering of the body's centre of mass is achieved, the deck is felt to be stationary and a considerable decrease in force on the sole of the stepping foot is experienced as stance is shifted to both feet.

The apparent downward motion of the platform when stepping onto it may be understood through the following considerations. When the body is raised onto the platform through contraction of antigravity muscles, for example, gastrocnemius and quadriceps, much greater muscular innervation is required than under terrestrial conditions because of the doubled weight of the body. The body does not rise upwards as rapidly as it would under terrestrial conditions with the level of motor innervation present; consequently, the relationship between muscle spindle activity and muscle length is altered with muscle spindle activity being abnormally high for the levels of α and γ motoneuron activation present. Abnormally high levels of spindle activity in a skeletal muscle relative to levels of α and γ coactivation are known to be decoded as a lengthening of the muscle and interpreted as movement of the limb(s) controlled by the muscle (Goodwin *et al.*, 1972). The apparent action of the limbs is in the direction that would be associated with lengthening of the involved muscles and is commonly attributed to motion of the substrate of support (Lackner and Levine, 1979; Lackner and Graybiel, 1981).

The unusually large force on the foot, the inappropriately slow upward motion of the body (signalled by visual, vestibular and somatosensory information) and the overestimation of the length of the antigravity muscles, are interpreted as due to the platform being pushed downward as a consequence of the subject's muscular exertion. Such a downward motion of the surface of suppport is also experienced during exposure to increased levels of gravitoinertial force when an individual does deep knee bends and rises from a squatting position (Lackner and Graybiel, 1981).

When stepping off the platform back onto the deck, the step feels abnormally hard and it also appears as if the deck has risen against the foot. This is to be expected since the force of contact on the sole of the stepping foot is much greater

TABLE 2. APPARENT SUBJECTIVE DISPLACEMENT OF BODY AND PLATFORM DURING STEPPING ONTO AND OFF STATIONARY PLATFORM UNDER TERRESTRIAL AND 2g GRAVITOINERTIAL ACCELERATION

	1 g acceleration level		*2 g acceleration level*	
	Self	*Platform/deck*	*Self*	*Platform/deck*
Step up	↑	0 cm	↑	↓ 5.3 ± 2.2 cm
Step down	↓	0 cm	↓	↑ 6.5 ± 2.6 cm

When subjects step onto and off a stationary 15 cm high platform under terrestrial levels of gravitoinertial acceleration (1 *g*), they experience only upward and downward motion of their own body. When the same motion is carried out against a 2 *g* acceleration background, the stationary platform seems to move downwards as they step onto it, and the deck seems to rise up and meet their feet as they step off the platform. Means and standard deviations of apparent displacements of platform and deck are presented, n = 6.

than it would be under terrestrial conditions for the rate at which the body is actually moving; moreover, the time to contact as the body is lowered is shorter than would normally be associated with the levels of innervation present in the antigravity muscles of the support leg. The increased force on the sole of the stepping foot stretches the gastrocnemius and quadriceps muscles, amongst others, producing momentarily an abnormally high level of spindle activity. This spindle activity is interpreted as an abnormal increase in muscle length and attributed to the deck rising against the sole of the stepping foot (*see* Lackner and Graybiel, 1981).

DISCUSSION

Our observations demonstrate that apparent body weight and perception of the forces acting on the body are the outcome of complex computations that minimally involve interrelating information about (1) the ongoing orientation of the body in relation to the gravitoinertial force vector, (2) the pattern of contact forces of support acting on the body, (3) the levels of α and γ motor activation in relation to levels of muscle spindle activity, (4) whether the body is accelerating in relation to its surroundings, and (5) whether objects are being carried. The perception of body weight is dependent on the sum of the contact forces supporting the body when it is not accelerating in relation to its surroundings nor carrying objects. Accordingly, we perceive our weight on Earth as being the same whether we are standing on two feet or one, and we perceive our weight as doubling when exposed to a 2 g background acceleration level regardless as to whether we are standing on two feet or one.

On Earth, perception of the forces acting on the feet (or on any other support surface of the body) is calibrated in terms of our 'normal' body weight. This calibration is such that nearly equal force is perceived on the supporting members (areas) of our body regardless of mode of support—seated, standing or lying down—although radically different pressures are associated with these postures because pressure is force per unit area. It is because of this active calibration or compensation that a great change in force or pressure is not perceived when shifting weight to one foot from two even though there is in fact a doubling of the force on the sole of the foot. The presence of the compensation becomes dramatically apparent when the normal pattern of forces acting on the body is increased twofold in the high-g phase of parabolic flight. Then, in shifting stance to one foot, an increase in force is experienced on that foot because compensation is only being made for 0.5 mg of the actual 1.0 mg increase in force on the stance foot; accordingly, an additional 0.5 mg 'residue' is perceived. Moreover, when we move about, the surface of support no longer seems stable because the relationship between the innervation of our muscles, the resulting patterns of afference, and the movements of our body, have been altered.

Such observations underscore the dynamic complexity of the processes involved in the control and appreciation of movement and posture. It is clear that this control involves monitoring and interrelating ongoing sensory and motor information from virtually all sensory and motor systems. Such monitoring and compensation enable us to maintain perceptual and postural stability as we move about and as we change mass in the course of development. Without this compensation, we would experience changes in apparent weight whenever the forces acting on our bodies changed through our own voluntary actions or through passive transport of our bodies. Instead, we perceive ourselves as being virtually weightless under normal terrestrial conditions and it is only when fatigued that we become aware of the considerable muscular forces necessary to move our body and limbs.

Put differently, we normally sense body mass rather than body weight, and we perceive mass as remaining constant. We do not perceive weight in the sense of the physicist's definition of weight, namely, weight equals mass times acceleration; rather, we tend perceptually to maintain mass constancy regardless of force background.

Ross (Ross, 1981; Ross and Bischof, 1981; Ross and Reschke, 1982) has shown that an object hefted with the hand is perceived as maintaining a near constant mass regardless as to whether the hefting is done under water or in the free fall or high force phases of parabolic flight. Under these circumstances, there are considerable differences in the muscular forces involved both with regard to moving the object and in moving the arm used to manipulate the object. In this context, it is notable that Fischel (1926) found that judgements of the weight of an object are quite independent of the muscles used in lifting the object and the specific movements of the involved muscles. Katz (1935) described experiments with patients who had undergone Sauerbruch amputations, in which an artificial limb was fitted and individual muscles were attached so as to allow considerable flexibility of movement. These patients showed remarkable accuracy in judging the weights of objects hefted with their artificial limbs. Such observations emphasize the importance of efferent and kinaesthetic factors in weight and mass perceptions, and the existence of dynamic sensory-motor calibrations related to background force levels.

It is important that these calibrations be dynamic because the mass and shape of the body change over time. This dynamic characteristic of skeletomuscular control can become apparent even in relatively brief exposure periods. We have found, for example, that over the course of a flight involving 40 parabolas, seated subjects gradually come to experience the increased gravitoinertial force periods as being less intense. It is apparent, therefore, that some degree of adaptation to increased weight is taking place within brief time spans (Lackner and Graybiel, 1982).

We expect that if a person were exposed to a 2 *g* background force level for a prolonged period, his sensory-motor control would become recalibrated for that force level and that he would no longer perceive an increase in force on his stance foot when shifting from two feet to one. On return to 1.0 *g* force levels we would expect the person to feel abnormally light. The opposite should happen after prolonged exposure to weightlessness in orbital flight and, in fact, we know that it does. The Skylab astronauts in postflight debriefings (*see* Johnston and Dietlein, 1977), described feeling more than twice as heavy as normal after return to earth; it took until the third day after splashdown before they again felt that they weighed the 'proper amount'.

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DISSOCIATION OF LANGUAGE AND COGNITION

A PSYCHOLOGICAL PROFILE OF TWO DISCONNECTED RIGHT HEMISPHERES

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SUMMARY

Two split-brain patients who differ in their right hemisphere language capacity were tested on a variety of simple cognitive tasks. Both isolated right hemispheres performed poorly on most tests. The results suggest that the presence of language in the right hemisphere, a brain system that ordinarily does not possess such competence, need not necessarily confer the full complement of cognitive skills associated with the language processing skills of the left hemisphere.

INTRODUCTION

A continuing challenge to the study of human cognition is an elucidation of how language processes influence cognitive, perceptual and mnemonic skills. Traditional approaches have included both the assessment of language disorders in adults and children (Lenneberg, 1967), as well as attempts to characterize language acquisition in children (Slobin, 1973). While these methods have provided a great deal of insight into human language function, conclusions regarding the dependence of cognitive processes on the presence of language are complicated by the possibility that language and cognitive processes could be evolving or deteriorating simultaneously in the subjects studied. Based on such observations, it cannot be determined how language as such interacts with and enhances general cognitive skills.

Certain aspects of this problem can be examined by studying the disconnected right hemisphere which normally does not possess language skills. In fact, in isolation following callosal section, the right hemisphere typically is unable to process language altogether (Gazzaniga, 1983). To date it has been observed that a right hemisphere without language is only minimally responsive to perceptual and cognitive testing. This finding characterizes the majority of split-brain cases and after postoperative assessment such patients are not usually followed neuropsychologically. While these patients' right hemispheres can detect simple stimuli and in some cases may be able to carry out specialized right hemisphere tasks such as visual constructional tasks (Gazzaniga *et al.*, 1965), their range of function has not been carefully documented. In the present context, however, none of the following tests could be carried out by patients in whom right hemisphere language was absent.

There is also a small subset of split-brain patients who do possess language in the right hemisphere, and it is of interest to assess what kinds of cognitive operations a right hemisphere that possesses language skills can carry out. The present report is centred on two patients, V.P. and J.W., who have been studied in our laboratory (Sidtis *et al.*, 1981; Holtzman and Gazzaniga, 1982). Both are part of a small group of patients in the national split-brain population who possess right hemisphere language, and one of them, V.P., also has the ability to access speech from the right hemisphere (Sidtis *et al.*, 1981; Gazzaniga, 1983). Examination of the cognitive capacities of these right hemispheres allows insights into what language confers to a brain system in terms of facilitating overall cognitive skills.

The present results suggest that a right hemisphere with language and the ability to access speech is slightly more capable of general cognitive ability than a right hemisphere with fewer language skills. At the same time, a right hemisphere with these language skills remains dramatically limited in general cognitive skills, and falls short of possessing the overall cognitive ability of the left hemisphere.

PATIENTS

J.W. is an alert 30-year-old right-handed male with a history of staring spells, reportedly since starting school. After his first grand mal seizure, the attacks became increasingly frequent and then intractable (Wilson *et al.*, 1982). Midline section of the corpus callosum was performed in two stages (Dr Donald Wilson, Dartmouth Medical School). The posterior half of the corpus callosum including the splenium was sectioned first, with the remaining anterior portion sectioned in a second operation ten weeks later.

V.P., a right-handed 29-year-old female, experienced recurrent seizures at 9 years of age. Anticonvulsant drugs controlled the seizures until 1979 when she began experiencing grand mal, petit mal, and myoclonic episodes while on multiple anticonvulsants. She underwent partial anterior callosal section in early April 1979, followed by complete section of her callosum in a second operation seven weeks later (Dr Mark Rayport, Medical College of Ohio).

METHODS

Special Tests of Cognitive Skills

A set of tests was administered to each hemisphere of J.W. and V.P. The overall objective was to determine whether the presence of right hemisphere language conferred the normal range of cognitive skills that usually accompany language function. Four tests, which are described in detail below, were selected for testing possible differences in cognitive capacity. One test, a measure of knowledge of current events, examined the simple capacity of each half-brain to learn new associations. The other tests all required the manipulation of two pieces of information and, therefore, a computation. One test each was selected from the verbal, mathematical and visual-spatial spheres of cognitive capacity.

All tasks described below involved lateralized presentation of visual stimuli. For pictures, the subjects were seated 1 m from a screen on which pictorial stimuli were projected from the rear and presented to the left or right of a central fixation point. The stimuli were displayed by means of a standard slide projector fitted with an electronic shutter. Stimuli were presented at least one degree to the right or left of fixation for 150 ms. For words, an Apple II Computer was used to display stimuli on a 15 inch monitor. The subject fixated a point at the centre of the screen and eye movements were carefully monitored. Before each test the subject was provided with extensive instructions and examples of the type of judgement required. These tests were run under free field conditions. During the practice trials the occasional incorrect responses were corrected and by the end of these trials the subjects were performing perfectly.

Language Profile

Both patients continue to be examined on their language capacity. In tests completed to date, the right hemispheres of both V.P. and J.W., as assessed by the Peabody Picture Vocabulary Test, possess a highly sophisticated lexicon which is essentially identical to the one they each possess in the left hemisphere. In addition, in a series of special tests it was determined that the right hemisphere semantic system can generate antonyms-synonyms, and superordinate as well as subordinate associations of lexical items. It is also equally proficient at all of the tasks in both the auditory and visual modality. V.P.'s right hemisphere, in addition to these skills, is able to carry out verbal commands, possesses syntactic abilities and can access speech. All these studies are reported in detail elsewhere (Gazzaniga, 1983; Gazzaniga *et al.*, 1983).

RESULTS

Inferential Capacity

Tests were performed to determine whether the right hemisphere could infer new meaning from the presentation of 2 different stimuli. In the first test, 8 pairs of pictures were flashed to either the left or right hemisphere. On each trial J.W. and V.P. were instructed to choose 1 picture out of 3 that best depicted the consequence of combining the 2 stimulus pictures. For example, a picture of logs and a picture of matches were sequentially lateralized and the free field choices were: a bonfire, a wood pile, and a lit cigarette.

The results of this test revealed different results for J.W. and V.P. In V.P. each hemisphere performed similarly with a score of 7/8 (88%). J.W. on the other hand was only able to perform the task with the left hemisphere (RVF: 7/8, LVF: 2/8, χ^2 corrected for continuity = 4.06, df = 1, $P < 0.05$).

In a second test of inferential reasoning, 2 words instead of 2 pictures were used for all test stimuli. An example of a trial in the test is as follows: the words 'water' and 'pan' were serially presented either to the left or the right hemisphere with an interstimulus interval of 1 s. Placed in front of the subject was a card with possible choices printed out. Prior to the presentation of the lateralized stimuli, the subject read aloud each word on the list. The choices for these stimuli were 'boil', 'melt', 'tan', 'swim', 'fry' and 'eat'. For each trial, a simple associative response was possible for each of the 2 words presented (for example, 'water' = boil or swim; 'pan' = boil or fry). There was, however, only one correct choice if the interrelation between the 2 stimuli was correctly inferred ('water' + 'pan' = boil). Each pair of stimuli was presented twice to each hemisphere, first with one word order and then the reverse order. There was a total of 40 trials to each hemisphere.

With words, J.W.'s right hemisphere was again unable to perform the task while the left hemisphere performed quite well (LVF = 12/40, RVF = 37/40). V.P.'s left hemisphere also performed well (38/40) but her right hemisphere performance dropped to 20/40 (chance = 16.6%). It appeared, however, that V.P.'s right hemisphere devised a strategy whereby she typically picked one of the 2 simple associations that went with the first stimulus word presented. For example, when 'water' and 'pan' were presented in that order to the right hemisphere, it would choose either 'boil' or 'swim'. When 'pan' and 'water' were presented in another condition, it would choose either 'boil' or 'fry'. In light of this observation, a performance of 50 per cent represents chance.

A third version of this test was administered to determine whether there is a difference between the picture/word and word/word testing method, especially for V.P. In this experiment a new set of 16 visual-pictorial and 16-word stimuli were developed for lateralized presentation to each half-brain. Four choices were possible for each test set. The experiment was first carried out with picture stimuli. For example, a picture of a person and a picture of a fish would be briefly flashed to either the left or the right hemisphere. The subject was then instructed to choose one picture out of a set of 4 that would best represent the inferred interrelation of the two stimuli presented. In this example the correct choice was a picture of a person fishing as opposed to a person bathing, water boiling or food frying. The stimulus card was placed in front of the subject before the presentation of each stimulus. The other pairs of lateralized picture stimuli that went with this response card were: person + water, water + pan, pan + fish.

In a follow-up session, the experiment was administered with lateralized word stimuli and the 4 pictorial choices. For example, the word 'person' and the word 'fish' would be presented and again the subject's task was to choose the picture that best depicted the concept to be inferred. Following this test, two control tests were carried out. In a test for memory function following presentation of the 2-word stimulus set, a card with the 4 possible stimulus words (e.g. person, water, pan, fish), was placed in front of the subject. The timing was such that it came when a response on the experimental trials had already been completed. The subject had to point to both words in order for the response to be scored correctly. In the second control test, the subjects were required to define the concepts to be inferred. Here the word 'fishing' was lateralized to either the left or right hemisphere and the subject was required to point to a picture of a person fishing as opposed to a person bathing, water boiling, or fish frying. The results are shown in Table 1.

Since the performances of both J.W. and V.P. did not differ significantly for the two presentation modalities, the results were combined. In both subjects the performance of the right hemisphere was significantly worse than that of the left hemisphere (V.P. $\chi^2 = 14.71$, $P < 0.001$; J.W. $\chi^2 = 15.94$, $P < 0.001$). At the same time, both right hemispheres could define the inferred concept. Also, both could remember the 2-item stimuli set over the time needed to solve the problem. Furthermore, in tests carried out on J.W., the right hemisphere could easily combine into meaning, compound words serially flashed to the right hemisphere. Thus such compound words as 'keyboard' flashed so that 'key' was seen followed moments later by 'board' found the patient was able to draw out a piano keyboard.

In all preceding test variations the difference between J.W.'s left and right hemisphere was consistently larger than the difference between V.P.'s left and right hemisphere. J.W.'s right hemisphere was unable to perform an inferential task in any of the modalities. V.P., on the other hand, appeared able to solve the problems in the first test. It is still not clear at this date whether or not V.P.'s initial good performance was more apparent than real.

TABLE 1. INFERENTIAL CAPACITY OF ISOLATED LEFT AND RIGHT HEMISPHERE

	V.P.		*J.W.*	
Stimulus condition	*LVF**	*RVF**	*LVF*	*RVF*
Lateralized picture/ picture choice	9/16	15/16	7/16	14/16
Lateralized word/ picture choice	9/16	16/16	7/16	15/16
Total	18/32	31/32	14/32	29/32
Defining inferred concepts	13/16	14/16	16/16	16/16
Memory for lateralized stimulus words	13/16	14/16	14/16	16/16

*LVF = left visual field. RVF = right visual field.

Mathematical Capacity

In a simple mathematical task, V.P. and J.W. were asked to 'add', 'subtract', 'divide' or 'multiply' a number singly presented to either the left or the right hemisphere. The free field choices were the numbers 1 to 20, 25 and 30 and placed on a card in front of the subject. Eight numbers were presented one at a time to each visual field for each of the mathematical functions. For example, each subject was instructed 'subtract one from the following number', and a number, say 8, was then presented to either the left or right visual half field. The correct manual response would be to point to the number 7 on the answer sheet.

The results are in Table 2. The left hemisphere was capable of the task, whereas the right hemisphere performed poorly at the mathematical operations even though V.P.'s right hemisphere could easily name all stimuli and J.W.'s could point on the answer sheet to each number presented. The difference between the hemispheres was significant for each subject (V.P.: $\chi^2 = 29.93$, $P < 0.001$; J.W.: $\chi^2 = 49$, $P < 0.001$).

TABLE 2. MATHEMATICAL SKILLS

	V.P.		*J.W.*	
	*LVF**	*RVF**	*LVF*	*RVF*
Pointing to answer				
Addition	3/8	8/8	0/8	8/8
Subtraction	3/8	8/8	1/8	8/8
Multiplication	1/8	8/8	0/8	7/8
Division	3/8	7/8	1/8	7/8
Reading numbers presented	16/16	16/16	Not possible	15/15
Pointing to numbers presented	16/16	16/16	15/15	15/15

*LVF = left visual field. RVF = right visual field.

Tests of Primary Mental Abilities

Each hemisphere of V.P. and J.W. was tested on their ability to solve simple concepts of spatial relations (adapted from the *Primary Mental Abilities Test*, 1962). Specifically, 16 geometric drawings of discrete designs were presented to either the left or the right hemisphere tachistoscopically. The task was to point to one of 4 possible drawings that best completed the design that had been lateralized. For every trial, the completed design made a square. These tests, while being possible to solve perceptually, also lend themselves to a verbal analysis.

Both V.P. and J.W.'s left hemispheres were significantly better than the right hemisphere at solving the problem (V.P.: RVF = 13/16, LVF = 7/16, $\chi^2 = 4.8$, $P < 0.05$; J.W.: RVF = 14/16, LVF = 8/16, $\chi^2 = 5.24$, $P < 0.05$).

Current Events

A test for current events from news headlines over the past two years was administered. The purpose of the test was to determine whether the right hemisphere, as well as the left, had acquired new information since the operation. In this test, a word was presented to either hemisphere and V.P. and J.W. were instructed to point to the correct answer out of 6 choices. For example, the word 'hostage' was presented and the choices were: 'Iran', 'Russia', 'England', 'Australia', 'Cuba'. Other current events questions were about the Olympics, the Royal Wedding, Skylab and the South-East Asian refugees.

Both V.P.'s and J.W.'s left and right hemispheres performed equally well on the test (V.P.: LVF = 39/55, RVF = 38/55; J.W.: LVF = 12/22, RVF = 13/20). The left and right hemispheres tended to miss the same questions.

DISCUSSION

The present study allows for observations of how the presence of language in a half-brain that normally does not possess such skills might enable it to carry out general cognitive acts such as mathematics, inferential reasoning and the acquisition of new general knowledge. The traditional view is that a brain system possessing language skills such as semantics and some syntax confers competence in cognitive processing in general (*see* Premack, 1983, for general discussion and debate). Results from the present study suggest otherwise. The striking failure of the right brain to make simple inferences, to carry out simple mathematical tasks, or to solve simple geometric problems stands in marked contrast to its ability to define words, learn new information, and even exceed left hemisphere performance on other specialized tests (Gazzaniga and Smylie, 1983).

Inferential reasoning might seem difficult if it were determined that the concept to be inferred was not represented in the brain system under study. Yet, in the present context, it was determined that the concept to be inferred from inspection of the 2-word stimuli was known to the right hemispheres of both J.W. and V.P. The failure in inferential reasoning was especially startling for V.P., since it has been demonstrated that her right hemisphere successfully grasps semantic relations, possesses some syntax and detects semantic incongruity as measured by the event related potential, N_{400} (Kutas and Hillyard, 1984).

The present results also stand in contrast to the level of cognitive competence seen in language trained chimpanzees as opposed to chimpanzees not given language training (Premack, 1983). Premack reports instances of inferential reasoning in the language trained chimp that could not be performed by the right hemisphere in the present cases. If these cross species comparisons are valid it raises the intriguing issues about the normal development of the right hemisphere. Clearly, it is a brain system that *can* perform such tests following early left hemispherectomy and, of course, in roughly half of the normal left-handed population. Yet, in the developing right-handed child, we suggest that it might be deferring problem solving and rational thinking to the left hemisphere during development. Upon testing of the right hemisphere as an adult, a situation uniquely made possible by split-brain surgery, the severe cognitive deficits of the right hemisphere are revealed.

It is also of interest to consider how the present results allow for fresh observations concerning the organization of semantic memory. There are some common assumptions in the research approaches used in the study of semantic memory. The most troubling is the notion that reaction time differences reflect properties of the semantic network (*see* Anderson and Bower, 1973). The view that longer reaction times reflect more complex processing within the semantic network may be in error. What seems more likely is that increased reaction times may emerge when computational systems other than those present in the semantic network have been activated for work on the task in question.

An alternative notion coming out of the present work is that when increased abstraction of language stimuli is required, these demands are met not by the language system itself, but rather by other cognitive systems that carry out computations on the language stimuli. In this view the ‘language system’ is considered to be a ‘dumb’ system that acts more as a simple data structure system. The so-called activities of language such as the facilitation of thought are to a large extent performed by other brain systems. This characterization of the relation between language and cognition would predict instances in which language is functional: thus the system could define language stimuli, and generate speech, but the organism could be totally impaired on general cognitive function. This condition, of course, commonly occurs in the early stages of cortical dementia (Joynt and Shoulson, 1979) and in subcortical dementia (Albert *et al.*, 1974).

It would appear that the conferring of language competence to a brain system does not necessarily mean that simple routine cognitive abilities are equally conferred. In the past, distinguishing how normal language is linked or not linked to other conceptual skills such as mathematics or inferential reasoning has been extremely difficult to analyse in the aphasic patient, since the lesion producing the language disorder could also be injuring other computational systems specialized for specific cognitive acts. The present results suggest that when these are dissociated such cognitive competencies are part of independent computational systems (*see also* Broadbent and Weiskrantz, 1982). Language usually reports on these computations with efficiency and accuracy, but the language system is not the system that is carrying out the activities.

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COLOURED PATTERNS IN HEMIANOPIC FIELDS

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SUMMARY

In a group of 96 patients with homonymous hemianopia or quadrantanopia from various causes, usually vascular lesions, 14 experienced coloured patterns in the hemianopic field. A questionnaire was used in an attempt to obtain as much information as possible on these phosphenes. They appeared in four major colours—red, green, blue and yellow—usually in fields that joined to form horizontally and vertically orientated geometric patterns. They demonstrated translocation related to ocular movement but otherwise were not influenced in any way by ocular movement or by opening and closing the eyes.

The patients experiencing these phosphenes constituted a homogeneous group in relation to neurological findings, cause of hemianopia, CT findings and prognosis. All had sustained cerebral infarction, and CT studies revealed small circumscribed lesions, usually subcortically in the striate area of the interhemispheric fissure and the adjacent white matter in the occipital lobes. The visual defects resolved completely or to a considerable extent in many cases, which suggests that the phosphenes are associated with hemianopia due to a functional disorder rather than to tissue loss. Coloured patterns are therefore a prognostically favourable symptom.

The geometric structure of the phosphenes and the fact that the same four colours consistently reappear must reflect the neuronal organization of the visual cortex. It can be postulated that this functional unit is organized on the basis of pyramids and tetrahedrons. The similarity of the geometric structures to the fortification lines encountered in migraine raises the possibility that the patterns are generated in the striate cortex. Absence of alteration in size with increasing distance from the fovea suggests that these phosphenes originate in a prestriate area. The colours reported indicate stimulation of intact colour-coding neurons in the prestriate area.

INTRODUCTION

A number of patients with homonymous hemianopia report phosphenes in the blind visual field, particularly in the early phase of the disorder. There are accounts of such phosphenes in the literature (Eskuchen, 1911; Horrax and Putnam, 1932; Teuber *et al.*, 1960; Gloning *et al.*, 1967; Lance, 1976), but the variety of descriptions given makes a clinical or pathophysiological interpretation difficult. Systematic clinical studies of the visual phenomena in hemianopic fields have not so far been reported. This is not surprising, since it is difficult to impose an organizing principle on the wide variety of descriptions of coloured and colourless phosphenes.

The following is an attempt at characterizing a particular type of phosphene which has been described with a high degree of uniformity by a large number of patients. These phosphenes may be termed coloured patterns. The phosphenes will be described in detail and their relationship to homonymous hemianopia discussed. In addition an attempt will be made to determine whether focal cerebral lesions are responsible for the appearance of these phosphenes. Finally the extent to which coloured patterns permit conclusions as to the nature and organization of the neurons generating these phenomena will be discussed.

PATIENTS

A total of 96 patients with homonymous hemianopia or homonymous quadrantanopia were examined over a period of five years. The distribution of visual field defects was as follows: right homonymous hemianopia, 36 patients; left homonymous hemianopia, 36; right upper field, 4; right lower field, 2; left upper field, 9; left lower field, 9. Most patients came to examination as a result of an acute visual disturbance. A minority (25 patients) presented with visual field defects dating from one to thirty-six years previously and were examined in the course of routine follow-up studies or were included on the basis of an incidental finding at neurological examination performed for other reasons. The onset of the visual disorder could not be determined in two patients. After neurological examination, ophthalmological studies were performed with special attention to the visual fields, visual acuity and foveal colour recognition. The visual fields were charted with a Goldmann perimeter and foveal colour recognition tested with Ishihara charts.

Table 1 shows the sex distribution and the aetiology of the visual disorder for the whole group. Cerebrovascular disorders were the most common cause. Cranial computed tomograms (CT scans) were made in almost all patients in order to determine the nature and location of the cerebral lesion, with electroencephalographic studies in some cases. Angiography was performed when indicated.

TABLE 1. AGE AND SEX DISTRIBUTION AND AETIOLOGY OF THE VISUAL DISORDER

Sex		*Age at first appearance*	*Cause*	
M	*F*			
61	35	18 to 83 years	Ischaemic stroke	68
			Space-occupying lesion	25
			Other	3

METHODS

Method of Evaluating the Phosphenes

In a preliminary examination, information was obtained on phosphenes from patients with homonymous hemianopia, after the patient's attention had been called to the possibility of such visual experiences. These interviews revealed that detailed information on phosphenes was only obtainable when the interviewer repeatedly asked about such events. A standardized interview would have been too rigid to produce results. Therefore a questionnaire based on relevant neurological and neurophysiological knowledge was developed in order to assist the interviewer in extracting as much information as possible on these visual phenomena. This questionnaire included 14 points. (1) When did the visual field defect or disorder of vision occur and when were phosphenes first observed? (2) During what period of time were visual phonomena observed? How long did the individual sensations last? (3) How often did the phosphenes occur and did they occur regularly? (4) In which part of the visual field were the phosphenes observed? (5) Did the phosphenes fill the entire visual field or were they limited to certain locations? Did they change their position from episode to episode or were they always found at the same location? (6) What shape did they have? (7) When more than one phosphene was observed at a time, were all similar in size? If they were of different sizes, where were the larger and smaller ones usually located? (8) Were they coloured or not? What colours? (9) Were the visual sensations similar? (10) Were single points of light or groups of points observed? When groups appeared did they seem to have a particular organizing principle? (11) Was it possible to influence the phosphenes in any way? (12) How did opening or closing the eyes influence the visual phenomena? (13) What happened to the phosphenes when the eyes were moved or when a near or distant point was fixed? (14) When were the phosphenes last seen?

Most of the patients were examined with a tangent screen at a distance of 1 m in order to localize the phosphenes in the visual field and to estimate their size. The patients fixed the centre of the screen and pointed out the position of the phosphenes with the hand and described the direction of movement in cases where this occurred. This method of demonstration proved useful in determining the position of the visual phenomena. The studies using the tangent screen also allowed a much more critical evaluation of the visual sensations. The patients repeatedly demonstrated a tendency to look in the direction in which the phosphenes presumably moved. When the midpoint of the screen was fixated the patients' statements on motion and direction of motion were much less certain. Some of the patients then expressed the opinion that the phosphenes had not moved at all. The subjects were then instructed to pay special attention to motion when phosphenes subsequently occurred. The patients were also requested to note the influence of eye movements on visual effects. However, the additional information obtained revealed nothing of major importance about the phosphenes.

The patients were initially asked to provide a spontaneous description of the colours observed during their visual sensations. They were subsequently requested to select the colours among the 16 different tones in Hering's (1920) colour wheel. The patients tried to estimate the size of the phosphenes on the tangent screen. Finally they were asked to make drawings of the phosphenes that they had observed. The results varied widely in quality, and some patients were incapable of drawing their visual sensations.

CASE REPORTS

Case 4

The patient, a man aged 72 years, was known to have had elevated blood pressure levels on occasions during the previous few years. While shaving one morning he experienced the sudden onset of dizziness and a temporary loss of vision lasting approximately one minute. After improvement in vision, spatial disorientation lasting approximately two hours was noted. The patient was free of symptoms on admission to hospital. The following night he was awakened by the sudden appearance of bright coloured spots on the left side. The figures were three-dimensional rhomboids with yellow, green, blue and red facets and appeared suspended in space. The rhomboids were joined in vertical chains, sometimes in multiple figures, and seemed to create a pattern. They always appeared in the upper portion of the visual field and descended slowly to the midpoint or below before moving to the left and disappearing. A few seconds later they reappeared at the same point and repeated their course. They always obliterated the visual field in their path. The repeated appearance of these blinking and flashing figures with their stereotyped motion disturbed the patient to such an extent that he notified the physician on call. He was seen by an ophthalmologist the next morning.

The patterns were smaller when the patient fixed a near point and larger when he fixed a distant point. The patterns changed position with eye movement, but opening and closing the eyes had no effect. The rhomboids appeared to measure approximately 0.5 deg on the tangent screen, and pure colours—red, yellow, green and blue—were selected from the Hering colour wheel. The patient was able to make very exact drawings of his visual experiences.

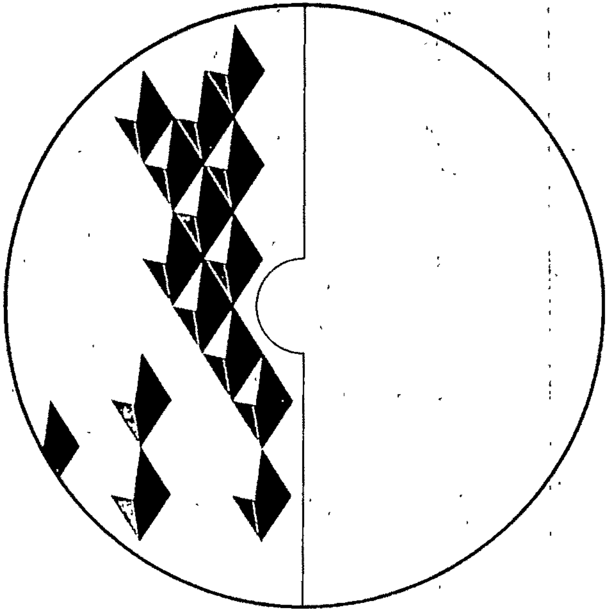

FIG. 1. Coloured pattern in the as yet unaffected left visual field of *Case 4*. Drawing by the patient. The sides of each pyramid were coloured red, yellow, green or blue.

The coloured figures subsequently appeared less often and disappeared completely on the third day of his hospital stay. At the same time an almost complete left homonymous hemianopia was found. There were no other abnormalities on neurological examination. CT scans revealed slight cortical atrophy and a hypodense zone in the right occipital lobe. An EEG recorded two days after disappearance of the visual phenomena revealed slight episodic activity but no focal changes. The hemianopia was unchanged. The descriptions of the phosphenes were identical one year later.

Case 9

The patient, a man aged 69 years, has suffered from hypertension for many years and diabetes mellitus, treated with oral medication, for eight years. A left hemiparesis from a cerebral infarct occurred at the age of 67 years. Restitution of motor function was almost complete. Intermittent claudication developed one year later, and aortofemoral bypass surgery was performed. At the age of 69 years another vascular lesion occurred resulting in a complete left homonymous hemianopia with sparing of the macular region. The EEG demonstrated focal activity in the right temporal area, and a CT scan showed a hypodense zone in the right occipital lobe. The patient described the initial visual disorder as follows. 'I woke up in the morning feeling well and turned to look at my wife who was lying to my left in bed. At first I could not see her at all. I had to turn my head far to the left to see her in bed. It was immediately clear to me that something was wrong with my vision on the left side. However, I was less disturbed by the loss of vision than by the appearance of flashes of coloured light on the left. These appeared as bright stars with all the colours of the rainbow, distributed over the otherwise dark left side; 4 to 8 figures flashed simultaneously for a period of several seconds and disappeared only to reappear immediately in the same pattern at another location. I sometimes had the impression that an entire net of colours appeared. The visual effect was so unpleasant that I decided to see an eye doctor.

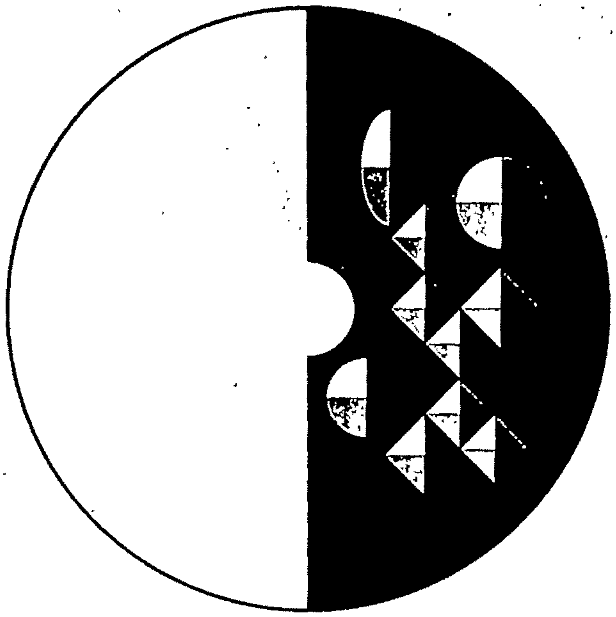

FIG. 2. Coloured pattern in the hemianopic right field of Case 12. The facets of each element were red, yellow, green or blue in colour.

The next day a coloured fog appeared a number of times for a period of several minutes on the right side. At that point I was admitted to hospital. Four days after their initial appearance the visual phenomena disappeared suddenly during an intravenous infusion.' The homonymous hemianopia persists unchanged.

Case 12

The patient, a 34-year-old nurse on an ophthalmology service, had never been seriously ill until she awoke one morning at 7 a.m. with a left-sided headache. At 10 a.m. she noticed that the right visual field was limited. Severely confused, she lost her sense of orientation in her own apartment. She decided to seek professional help two days later, driving her own car and following a number of detours to arrive at the ophthalmologist's office. A right homonymous hemianopia with macular sparing was diagnosed. Neurological examination failed to demonstrate other abnormalities. CT scans with contrast enhancement revealed a slightly hyperdense zone in the left occipital region. The history, the physical findings and the fact that the neurological deficits improved continuously over a period of fourteen days with full restitution of visual capacity suggested a diagnosis of cerebral infarction.

Approximately two to three hours after the patient noticed her visual field defect, bright silver stars suddenly appeared in the dark field, especially in the upper segment. In addition, the patient saw a group of bright coloured spheres, ellipses, squares and hexagons which appeared in the upper left of the dark field and traversed the field only to disappear suddenly as though they had passed behind a black wall. The patient observed this phenomenon 8 to 10 times per day, with individual sensations lasting for a fraction of a second repeated during a period of one to two hours. The figures had four intense colours. Without hesitation she selected the four pure colours from the Hering wheel. She estimated the size of the individual ellipses, squares and hexagons between 2 and 5 deg on the tangent screen. She did not report an apparent change in size with increasing distance from the screen. The phosphenes moved with eye movements. They were unchanged by opening and closing the eyes. After three days the coloured patterns disappeared completely.

RESULTS

Of the 96 patients, 40 experienced phosphenes in the hemianopic field. They perceived several different visual phenomena during the course of their illness. Coloured phosphenes were reported by 26, 17 described phosphenes with heterogeneous colours and shapes and 14 reported visual phenomena which can be classified as coloured patterns.

All 14 patients described several different colours, usually four, less often two, three or five. They selected intense yellow, red, green and blue from Hering's colour wheel; 2 patients also selected orange and one identified violet. The colours were so intense that the patients initially closed their eyes in an attempt to shut out the light. One patient described his phosphenes as though a light as powerful as the sun had projected the colour, while another patient spoke of 'shocking' colours and a third likened the visual effect to fire, which expresses the painfulness of the visual experience.

The patients were usually able to describe the shape as well as the colours of their phosphenes. Comparisons were repeatedly made with a kaleidoscope held against the sun, a snakeskin, a tortoise shell, a harlequin's suit, a brightly coloured net, a cloud of burning phosphorus, or the tread of a tyre. The colours did not appear sequentially but usually simultaneously and in a constant pattern. Two patients, however, described a bright point which emitted rays of yellow, red, blue and green

TABLE 2. SYNOPSIS OF CLINICAL DATA FROM 14 PATIENTS WITH COLOURED PATTERNS

Patient	*Age at onset of hemianopia*	*Age at examination*	*Sex*	*Homonymous hemianopia*	*Visual acuity*		*Improvement of hemianopia*	*Coloured patterns*	*Localization*	*Aetiology*
					L	R				
Case 1	68	68	F	L	0.5	0.6	–	+	O	I
Case 2	40	40	M	R	1.2	1.2	+	+	O	I
Case 3	71	71	F	L	1.0	1.0	+	+	O	I
Case 4	72	72	M	L	1.0	0.9	+	+	O	I
Case 5	51	51	M	L	1.2	1.2	+	+	O	I
Case 6	57	57	M	L	1.0	0.9	+	+	O	I
Case 7	77	77	M	R	1.0	1.0	+	+	O	I
Case 8	35	54	F	R	1.0	1.0	–	+	O	I
Case 9	69	69	M	L	0.7	0.7	–	+	O	I
Case 10	59	61	M	L	1.0	1.0	+	+	O	I
Case 11	63	63	M	R	1.0	1.0	+	+	O	I
Case 12	34	34	F	R	1.2	1.2	+	+	O	I
Case 13	62	62	M	R	1.0	1.0	+	+	O	I
Case 14	66	66	F	L	1.0	1.0	–	+	O/P	I

O = occipital; P = parietal; I = cerebral infarction light. In these cases, yellow was observed initially, followed by the other colours, which were always quite distinct from one another. Together they described a figure that was most often angular, usually in the form of a star, a honeycomb, a triangle, pyramid or tetrahedron, and rarely a round form such as a circle or an ellipse. Several patients described a pattern floating in space. Most of the phenomena contained a basic figure which almost always combined to form patterns which led to the use of the terms honeycomb, harlequin's suit, snakeskin, tortoiseshell, kaleidoscope or net. Horizontal and vertical lines predominated.

It was apparently difficult for the patients to estimate the size of the phosphenes. When a tangent screen was used at a distance of 1 m, estimates of the size of basic elements ranged from 0.5 to 8 deg. The patients noted no apparent relationship between the size of the phosphenes and distance from the fixation point, except Case 4. In general the phosphenes did not vary in size from episode to episode in the same subject. However, basic elements were sometimes eradicated from the pattern before the entire figure disappeared. The phosphenes never filled an entire half-field.

The coloured patterns appeared suddenly and usually did not move. Initial motion was slow and lasted only one to two seconds when it occurred. Three patients reported that the phosphenes appeared high in the blind field and descended to the midline before they disappeared in the lateral or lower part of the field. It may be assumed that this represents genuine motion, since movement of the phosphenes in the visual field was independent of eye movement. Opening or closing the eyes never affected the phosphenes.

The 14 patients who perceived coloured patterns suffered an acute homonymous hemianopia. Quadrantanopia was not found at the onset of the visual disorder. The phosphenes occurred shortly after development of the hemianopia. They were observed simultaneously with the visual field defect in 6 patients and between one and three hours after the initial deficit in 3 other patients. Five subjects reported phosphenes before development of the hemianopia. Case 4 described quite impressively the manner in which the phosphene—similar to the scintillating scotoma experienced in ophthalmic migraine—seemed to impose itself between the viewer and objects in such a way that he was not able to see behind the phosphene. Visual capacity was restored when the phosphene disappeared. This patient and two others (Cases 1 and 14) reported that the phosphenes disappeared with the development of the visual field defect. In most cases the phosphenes disappeared within ten days of the onset of hemianopia, though they lasted fifteen days in one patient (Case 10). Fig. 3 summarizes the period of time over which coloured patterns were observed, as well as the temporal relationship of these phosphenes to the onset of hemianopia.

Ten of 14 patients experienced improvement in the visual defect, usually within four weeks. Of the 3 patients in whom appearance of phosphenes preceded the onset of the visual disorder and disappeared with the development of hemianopia (Cases 1, 4 and 14), 2 reported no improvement in the hemianopia while one (Case 4) showed slight improvement in the upper quadrant. Vision returned to normal in

3 patients (Cases 2, 11 and 12), and 4 others (Cases 3, 6, 10 and 13) showed significant improvement (fig. 4). Visual acuity was not affected by the disorder, and there were no derangements of colour description, colour perception or foveal colour discrimination. No patient suffered a neuropsychological disorder such as aphasia, alexia, agraphia, prosopagnosia or spatial disorientation.

A vascular disorder in the occipital lobe was found in all patients. CT studies were made in 11 patients, and infarction in the occipital lobe was demonstrated in 9 of these. The CT appearances failed to reveal changes which might explain the clinical findings in 2 patients (Cases 2 and 12), both of whom demonstrated complete recovery of vision. The hypodense zones were small in the majority of patients, and the prestriate cortex was not affected visibly in a single case. The lesions were more often at a subcortical level affecting the optic radiation. With the exception of one patient (Case 14) who also had formed hallucinations, the cortical lesions were limited and only involved a small portion of the primary visual cortex.

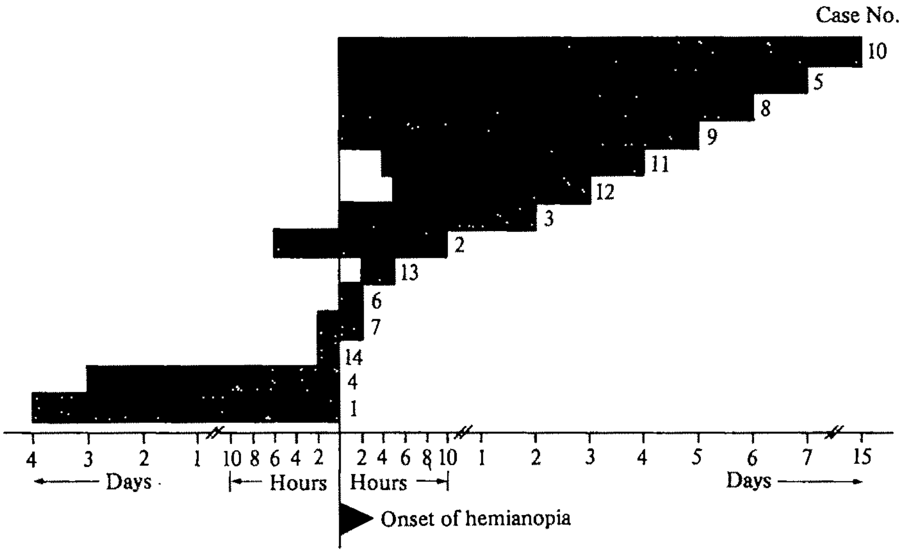

FIG. 3. Period over which coloured patterns were observed and relation to the onset of homonymous hemianopia.

DISCUSSION

The characteristics of the coloured patterns may be summarized as follows. They appear in four major colours—red, green, blue and yellow—usually in fields that join to form horizontally and vertically orientated geometric patterns. They appear suddenly, usually only for a fraction of a second, and remain in one position, although they may move slowly and stereotypically within the hemianopic field in a minority of cases.

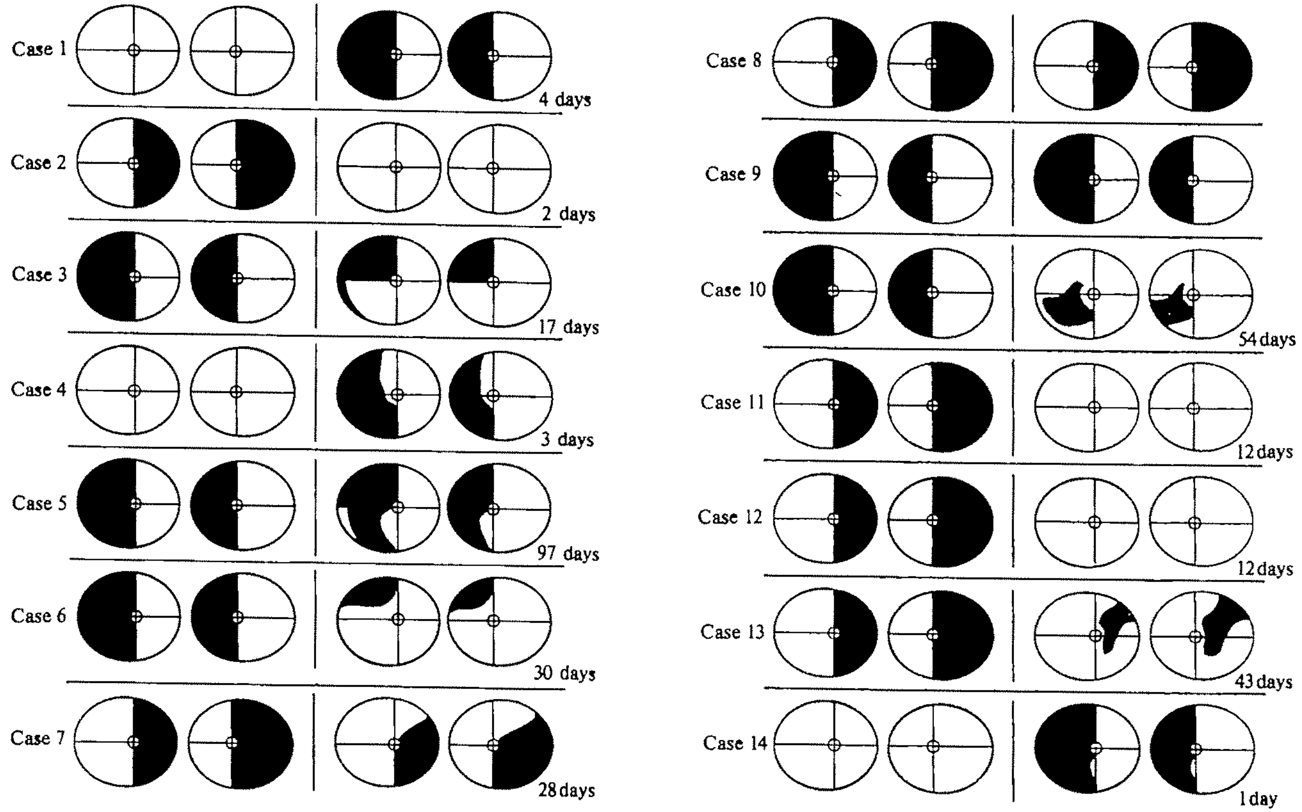

FIG. 4. Visual fields in 14 patients experiencing coloured patterns. *Left*, visual fields at onset of the disorder. *Right*, ultimate shape of the visual field defect and time after which no further change occurred. (Detailed analysis of macular vision was not performed.)

The reports by other authors on phosphenes in hemianopic fields are not detailed enough to permit adequate comparison. It is likely that the phosphenes reported by Higier (1894) and Eskuchen (1911), by Gloning *et al.*, (1962) in a series of patients with brain infarction, and by Mooney *et al.*, (1965) in a study on the recovery phase of homonymous hemianopia, are identical with our series. Case reports by Wilbrand and Saenger (1917) documented comparable phosphenes. For example, one 40-year-old patient with cerebral infarction 'complained of strong visual effects which appeared as flickering flames, zig-zags, serpentine lines and lightning flashes which caused him considerable discomfort. The visual effects were strongest immediately after the cerebrovascular accident and lasted approximately 10 to 12 days.' Similar phenomena are apparent in the case reported by Kinsbourne and Warrington (1963). A patient with homonymous quadrantanopia secondary to brain infarction in the occipital lobe experienced bright multicoloured flashes of light which were at times without apparent order but which at others resembled fortification figures. Krause (1924) described patients who experienced coloured patterns in the hemianopic field for a short period following resection of occipital lobe tumours. None of the phosphenes provoked by electrical stimulation of the occipital lobes resemble the coloured patterns described above (Foerster and Penfield, 1930; Penfield and Perot, 1963; Brindley and Lewin, 1968; Dobelle *et al.*, 1979).

The phosphenes usually appear at the onset of hemianopia, but may precede the event by hours or, in some cases, days. When phosphenes occur a functional disorder of the entire visual cortex or a portion thereof, may be assumed, rather than an irreversible tissue defect. It implies that restitution of visual capacity is possible as long as the phosphenes are observed. If the coloured patterns disappear before vision improves—recognizable on the basis of grey tones in the blind field or perception of crude movement—then major visual improvement is unlikely; the visual disorder is secondary to a persistent tissue defect. Twelve of the 14 patients perceived coloured patterns in the hemianopic field; 10 of them showed an improvement of the visual field defect. The control group consists of those patients who also developed a homonymous hemianopia from a stroke but who did not report phosphenes in the hemianopic field. This comprises 38 patients, of whom only 16 showed improvement in the visual field defect. These results underline the favourable prognosis of coloured patterns.

Coloured patterns seem to occur mainly in the course of a cerebrovascular event. Similar phenomena have been reported in cases of tumour, abscess or craniocerebral injury in the occipital region, but these reports usually involve visual manifestations in epileptic seizures rather than isolated phenomena in the hemianopic field. Case reports by Westphal (1881) and by Henschen (1923) emphasize this point.

The significance of coloured patterns in localizing lesions is based on the results of clinical examination as well as on CT findings. Homonymous hemianopia without other neurological or neurophysiological deficits after the first four hours suggest a lesion located in the posterior portion of the optic radiation or in the area striata.

CT studies revealed that most lesions were in the terminal part of the optic radiation, especially within the region of the area striata. The occipital cortex deep in the interhemispheric fissure and occipital convexity were usually not noticeably involved in CT studies (fig. 5).

The extent to which the particular characteristics of the coloured patterns, their strict geometric figures, and conspicuous colours allows conclusions as to the cortical area in which they originate, above and beyond the information provided by clinical examination and computed tomography, will now be considered. The four colours most often described are the 'primary colours' which form the basis of colour codification in Hering's (1920) theory. It may be assumed that the appearance of these colours in phosphenes without an adequate external stimulus indicates stimulation and/or inhibition of the same neurons at a corresponding presentation in the visual hemifield. It could be suggested that neuronal stimulation occurs generating the colours in the phosphenes, especially in area V4 where Zeki (1973) found a conspicuously large number of colour-coded cells in his experiments on monkeys. Unfortunately it is as yet unclear whether these topographic and neurophysiological findings, which have been subject to recent criticisms (Schein *et al.*, 1982), are applicable to the human brain. For example, area 17 (V1) in man is located for the most part in the occipital portion of the interhemispheric fissure, while the same area extends well over the cortical convexity in the monkey.

If it is assumed that the colour-coded neurons in area V4 described by Zeki (1973) are in fact responsible for colour perception and that these results are valid for the human brain, then it follows that a lesion in these neurons would cause a corresponding deficit. However, the lesions described by Damasio *et al.* (1980) in their two patients with acute hemiachromatopsia or complete achromatopsia are located in the lingual and occipitotemporal gyri, rather far from the area corresponding to V4 in the human brain. In an attempt to explain this discrepancy Damasio and coworkers (1980) postulated that colour-coded neurons are concentrated in a wide belt within the prestriate area. As far as phosphenes are

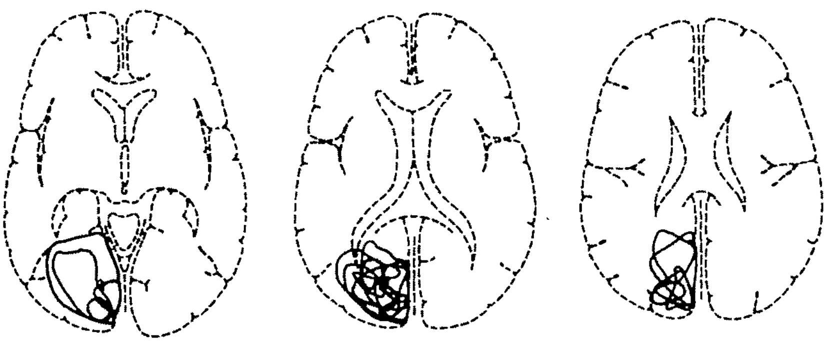

FIG. 5. Superposition of computed tomograms from 9 patients with coloured patterns in the hemianopic field. All zones of lesions projected in the left occipital lobe. (The illustrations contain the slices which represent the largest portion of the occipital lobes (McAuley and Ross Russell, 1979). Slices through the pineal region, as well as 10 and 20 mm higher.)

concerned, these results suggest that the colour phenomena result from stimulation of colour-specific neurons in a large area of the visual association cortex.

It is as yet unclear why the colours appear in such strictly geometric patterns, since experimental studies have revealed that colour-coded neurons are nonorientated. Hubel and Wiesel (1968, 1972) did find orientated receptive neurons in the striate and prestriate area. It might be concluded that the initial stimulus generating coloured patterns originates in geometrically organized orientated receptive neurons in the striate or prestriate cortex with subsequent extension to colour-coded neurons in the prestriate cortex in accordance with strict principles governing perception of the four primary colours. The fact that phosphenes may appear before the onset of hemianopia and that they represent prognostically a favourable symptom support the assumption that a large number of intact and functionally competent neurons must remain within the striate and prestriate cortex.

Another morphological characteristic of the coloured patterns deserves special emphasis. The vertical boundaries of the pyramids or tetrahedrons have striking similarity to the fortification lines observed in migraine attacks. The latter are interpreted as resulting from patterns of stimulation and inhibition in the field of macular representation extending over the cortex in area 17. Richards (1971) connected hypothetically the tips of the fortification lines and concluded that the resulting hexagonal patterns corresponded to the functional architecture of the striate cortex. The coloured patterns described by our patients suggest a functional neuronal architecture based on pyramids or tetrahedrons.

The fact that visual phenomena in migraine increase in size as they wander from the fovea to the periphery of the visual fields is explained by differences in size of the various receptive fields (Cowey and Rolls, 1974; Dobelle *et al.*, 1979). If it is assumed that the stimulus for coloured patterns as fortification lines originates in area 17 then it is surprising that the patients described the patterns as strictly regular without any change in size within the individual figures (pyramids or tetrahedrons). It would be expected that the individual figures are small within the cortical area of foveal representation but increase in size with increasing distance from the fovea. The patients did not describe such changes in size. However, since the coloured patterns appeared for a fraction of a second, observations of this nature would require special skill. If the pyramids or tetrahedrons fail to demonstrate an increase in size from the centre to the periphery of the visual field, as the patients reported, then the visual phenomena might be generated by groups of neurons within an area which is not subject to the special properties governing area 17.

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SOMATOSENSORY EVOKED POTENTIALS FOLLOWING MEDIAN NERVE STIMULATION

I. THE CERVICAL COMPONENTS

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SUMMARY

Median somatosensory evoked potentials were studied in 20 normal adult volunteers. Recording electrodes were positioned over posterior, anterior and lateral neck, as well as on the scalp.

Three distinct cervical potentials were identified. Immediately after the afferent volley passes Erb's point, a travelling wave is recorded in the lateral cervical electrodes ipsilateral to the side of stimulation. This represents the afferent volley approaching the spinal cord in the proximal brachial plexus and cervical roots and has been designated the 'proximal plexus volley' (PPV). Following PPV, a second travelling wave is recorded which increases in latency from low to high cervical levels. It represents the afferent volley in the dorsal column, and has been designated the 'dorsal column volley' (DCV). Following DCV, a stationary potential, designated CERV N13/P13, is recorded with characteristics of a transverse midline dipole having maximal negativity posteriorly and maximal positivity anteriorly. This potential may be generated by interneurons in the dorsal grey of the cervical cord.

Each of these cervical travelling waves is accompanied by a negative far-field potential recorded at the scalp. The PPV is accompanied by a negative scalp deflection with a nominal latency of 10 ms (N10), and the peak of DCV at SC_1 is accompanied by a scalp negativity with a nominal latency of 12 ms (N12).

In view of these observations, it is necessary to reexamine assumptions regarding the polarity of scalp-recorded potentials generated by remote neural events.

INTRODUCTION

Despite published reports from a number of different laboratories (*see* Cracco, 1973; Chiappa *et al.*, 1980; Desmedt and Cheron, 1980; Lueders *et al.*, 1983), there is still uncertainty as to the origins of short latency somatosensory potentials evoked by median nerve stimulation in man. To a large extent, these difficulties derive from ambiguities inherent in the data. Signals recorded from scalp and neck electrodes represent the complex algebraic summation of waveforms reflecting concurrent activity in multiple neural generators. In this setting, it is not surprising that variations in recording techniques have contributed to lack of agreement among investigators. In addition, interpretations of far-field components have been influenced by prior assumptions regarding the polarity of potentials recorded at a distance from their presumed sources. In this paper, we examine the early subcortical components of the median somatosensory evoked potential (SEP) as recorded from both cervical and scalp electrodes. We present evidence that appropriately placed cervical electrodes register two travelling waves, the first corresponding to the afferent volley in the proximal brachial plexus or roots, and the second corresponding to the ascending dorsal column volley. These travelling waves are recorded as two negative transients by scalp electrodes.

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METHODS

SEPs were recorded following stimulation of either right or left median nerve in 20 volunteers (19 men) ranging in age from 18 to 32 years. The study was approved by the Institutional Review Board of Columbia-Presbyterian Medical Center and informed consent was obtained from each participant. Subjects lay supine in a quiet, darkened room. Oral diazepam was given to promote muscle relaxation and sleep.

Stimuli were 0.2 ms square wave electrical pulses delivered at a rate of 4/s through electrodes placed over the median nerve at the wrist. The cathode was positioned 2 cm proximal to the anode. Stimulus intensity was adjusted to elicit a consistent twitch of the thumb without producing discomfort. Scalp electrodes were positioned in midsagittal and coronal arrays through Cz in accordance with the international 10-20 system. An additional Cz′ electrode was interposed mid way between Cz and Pz. Electrodes were placed over the first to seventh cervical vertebrae (designated SC_1 to SC_7). Anterior cervical electrodes were evenly spaced in the midline from the sternal notch to the superior border of

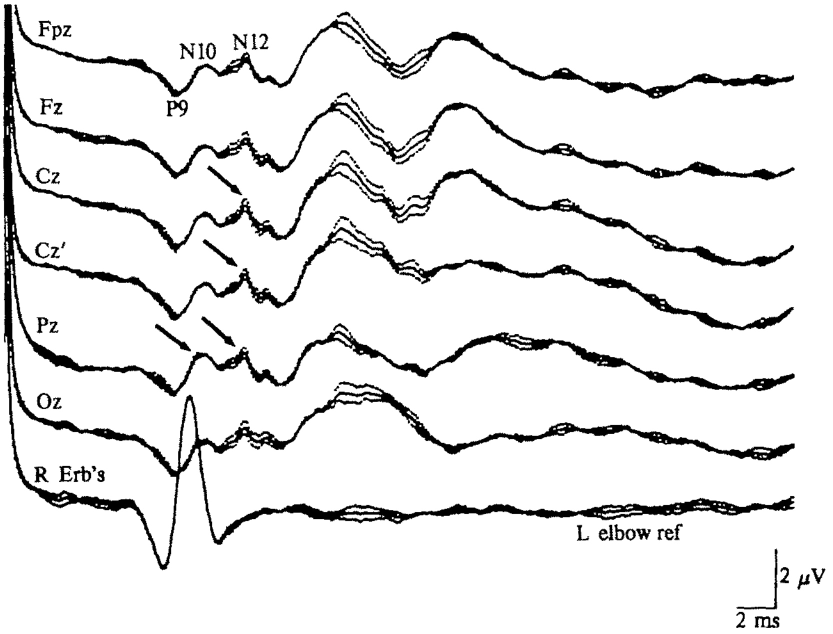

FIG. 1. SEP following right median nerve stimulation recorded in the midsagittal plane. Arrows indicate where N10 and N12 potentials exceed baseline.

the thyroid cartilage (*see insert diagram*, fig. 5). Three lateral cervical electrodes were vertically spaced along the anterior border of each sternocleidomastoid muscle (*see insert diagram*, fig. 3). Additional electrodes were applied to the neck to form a ring of eight equally spaced electrodes at the level of SC_5 (*see insert diagram*, fig. 6). An electrode on the elbow or knee contralateral to the side of stimulation was used as a noncephalic reference. Contact impedance was maintained at 3000 ohms or less.

Eight channels of evoked potential data were recorded simultaneously using a computer with an analog to digital converter operating in a multiplexed mode at a conversion rate of 10000 samples per second per channel. Amplifier gain was 100000, and −6 dB high and low pass filter settings were 30 and 3000 Hz, respectively. Data were acquired for a period of 40 ms following each stimulus, and 1000 to 4000 responses were averaged for each trial. Responses with excess artefact were automatically excluded. Each trial was repeated at least once, and the replicated trials along with a grand average were superimposed graphically to demonstrate reproducibility. No form of curve smoothing was used.

All recordings were obtained from cervical or cephalic 'active' electrodes referred to noncephalic sites, and response waveforms were designated by their polarity at the 'active' electrode (upward deflection negative) and their nominal latency. All latency measurements are given as mean ± 1 SD.

RESULTS

Early Scalp-recorded Potentials

Following median nerve stimulation, all scalp electrodes record similar early waveforms (figs. 1, 2). Initially all electrodes register a positivity, P9 (9.4 ± 0.6 ms). During the 4 ms interval following P9, two widely distributed scalp negativities are

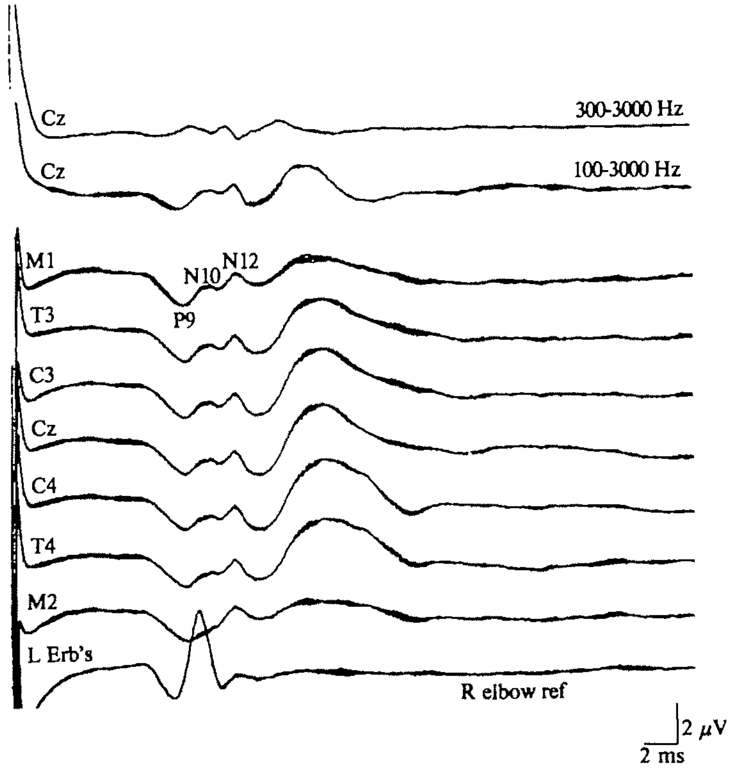

FIG. 2. SEP following left median nerve stimulation recorded in a coronal plane through Cz. Except where indicated, −6 dB low and high frequency filter settings of 30 and 3000 Hz, respectively, were used. Increasing the low frequency filter to 100 and 300 Hz enhanced the N10 and N12 negative deflections making it unlikely that excursions above baseline are due to an underlying negative baseline shift. The latency shift of N10 and N12 in the first channel is the consequence of a 300 Hz low frequency filter.

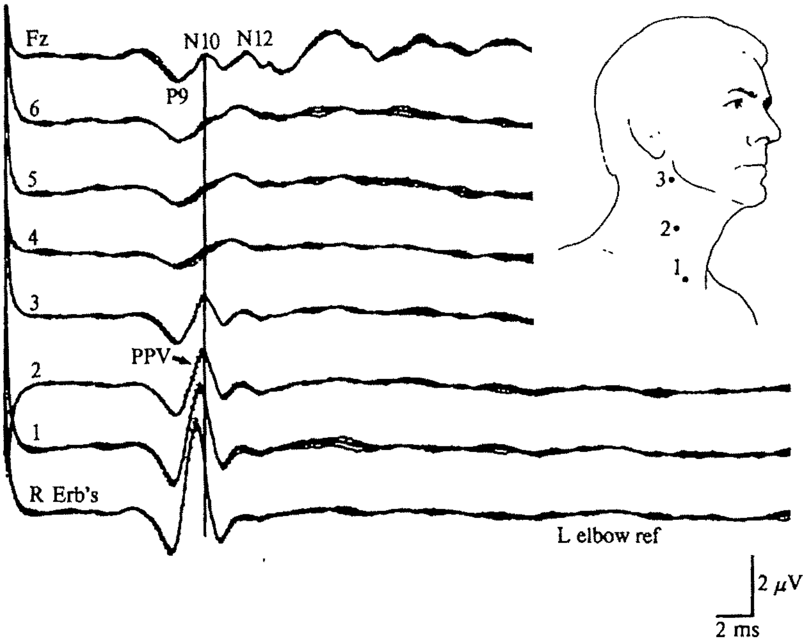

FIG. 3. Right median SEP recorded from electrodes vertically spaced along the anterior border of each sternocleidomastoid muscle referenced to left elbow. (Electrodes 4–6 are on the left side and correspond to electrode positions 1–3 shown on the right in the insert.) After the afferent volley passes Erb's point, a travelling wave (PPV) is seen on the right but not on the left. PPV is accompanied by a negative scalp deflection, N10.

recorded: N10 (10.7 ± 1.0 ms) and N12 (12.7 ± 1.0 ms). These deflections represent true negativities rather than mere return of the preceding positivities to baseline since, in some channels (fig. 1, arrows), these components exceed the preceding baseline. The negative deflections were enhanced rather than diminished by raising the low frequency filter setting from 30 to 100 and 300 Hz (fig. 2), thus making it unlikely that the excursions above baseline could be caused by an underlying slow negative baseline shift. This was consistent from trial to trial and between test sessions. While these potentials occur widely over the scalp, their distribution is not uniform. In all subjects, N10 was significantly attenuated or absent at the contralateral mastoid electrode.

Neck-recorded Potentials

Immediately after the afferent volley is recorded over Erb's point (10.0 ± 0.9 ms) a travelling wave of similar waveform and polarity appears at electrodes vertically situated along the anterior border of the ipsilateral sternocleidomastoid muscle (fig. 3). This volley is either absent or only poorly reflected in electrodes similarly positioned over the contralateral neck. Since this lateralized potential immediately follows the Erb's point potential, it must represent activity occurring proximal to

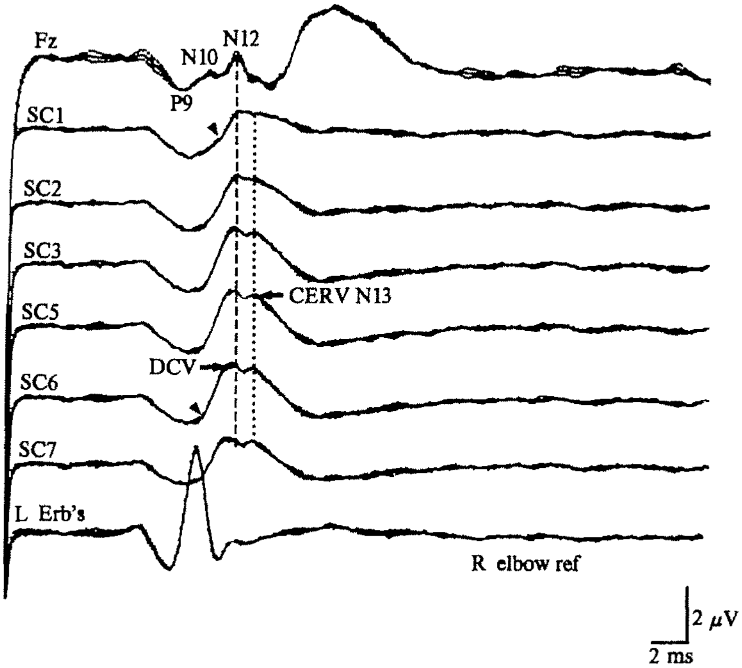

FIG. 4. Left median SEP recorded from Fz and from electrodes spaced vertically along the posterior neck in the midline. Two distinct negativities are seen. One is a travelling wave which corresponds to the dorsal column volley (DCV), and the other (CERV N13) is a stationary potential.

Erb's point, that is in the trunks of the brachial plexus or cervical roots. We designate this the 'proximal plexus volley' (PPV). The scalp recorded N10 potential coincides with PPV (fig. 3).

Following PPV, a second cervical negativity is recorded from electrodes over the posterior neck in the midline. Its latency increases progressively from low to high cervical levels (fig. 4). Since it has the characteristics of a travelling wave ascending in the cervical cord, we refer to it as the 'dorsal column volley' (DCV). The scalp-recorded N12 occurs simultaneously with the peak DCV negativity at SC_1 (fig. 4).

Following the DCV, posterior cervical electrodes record another negativity (fig. 4) which we designate CERV N13. The latency of CERV N13, unlike those of PPV and DCV, does not vary with electrode position. Its amplitude is position dependent, however, and attenuates rostrally. A simultaneous positivity (CERV P13) is recorded from midline electrodes placed over the anterior neck (fig. 5).

The topographic relationship of the different cervical potentials is further illustrated in fig. 6. Electrodes were placed in a ring about the neck at the level of SC_5 posteriorly and the superior border of the thyroid cartilage anteriorly. PPV is recorded from the anterolateral and lateral neck electrodes on the side of stimulation (F and E), and with slightly diminished amplitude in the anterior

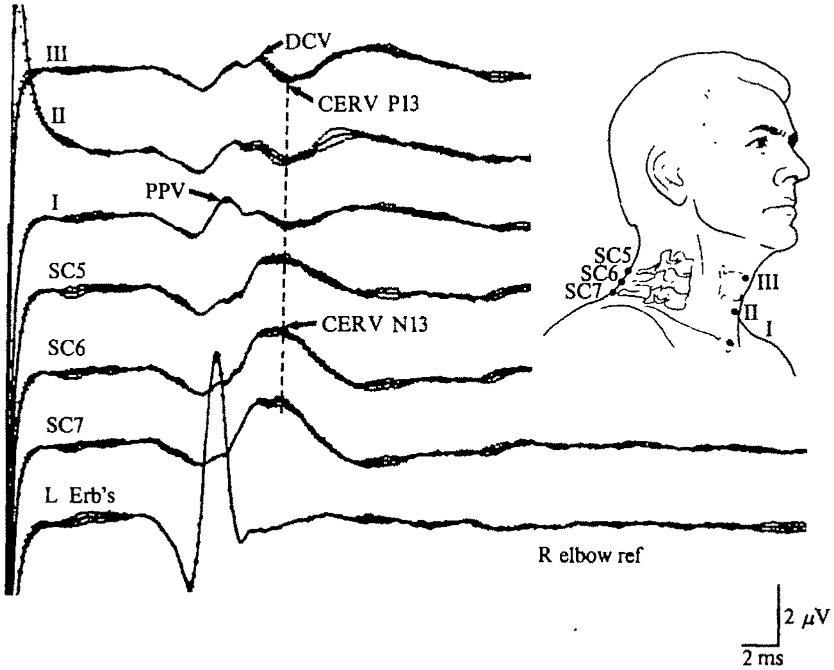

FIG. 5. Right median SEP recorded from electrodes over anterior and posterior midline cervical electrodes. CERV N13 posteriorly is synchronous with CERV P13 anteriorly. DCV is visible in both sets of electrodes, although it tends to merge with CERV N13 posteriorly.

midline (D). PPV is not recorded to any significant extent contralateral to the stimulated side. CERV N13 is maximal posteriorly (SC_5), and CERV P13 is maximal anteriorly (D). These potentials attentuate posterolaterally and anterolaterally respectively. While DCV is present in all electrodes, its appearance is influenced by the antecedent and succeeding potentials. DCV is best seen in isolation in a midlateral electrode, opposite the stimulated side (B), where its appearance is unaffected by PPV, and where CERV N13 and CERV P13 are smallest.

DISCUSSION

The Proximal Plexus Volley

The contribution of nerve trunk and root activity to cervical and scalp-recorded evoked potentials has received limited attention. Based on geometric considerations, Desmedt and Cheron (1980) speculated that an electrode located on the C7 spinous process would preferentially record afferent activity in the C6-C7 roots rather than the ascending dorsal column volley. Yamada *et al.* (1980) reported that low cervical electrodes, positioned 5 cm lateral to the midline on the side of the

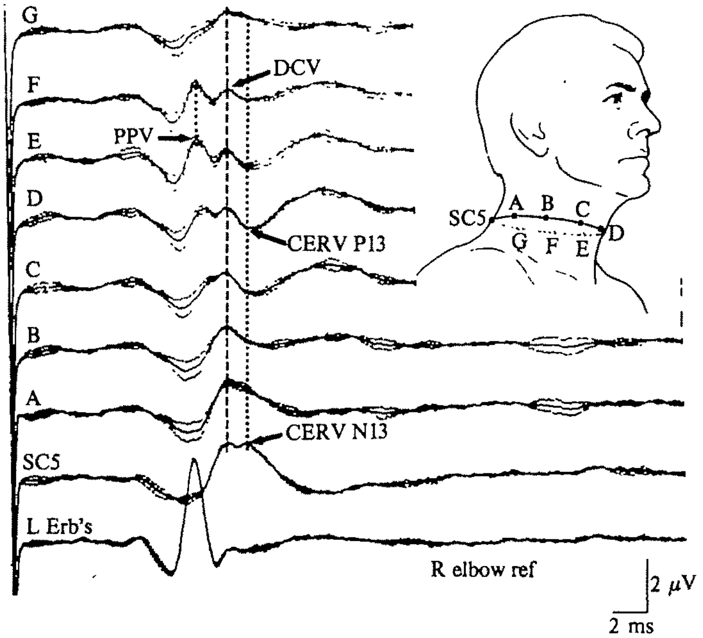

FIG. 6. Left median SEP recorded from electrodes positioned in a circle around the neck at the level of SC5 posteriorly and above the thyroid cartilage anteriorly. The topographical relationships of PPV, DCV, and CERV N13/P13 are illustrated.

stimulus, registered a negativity, 'N11', that was not seen by a similarly placed contralateral electrode. They observed that their 'N11' was of slightly shorter latency in lateral neck derivations than when recorded in the midline, and suggested that this potential represented a travelling wave approaching the cord. Although no illustration of this phenomenon was provided, Yamada *et al.*'s 'N11' would seem to be identical with our PPV.

The extent to which PPV is present in posterior midline neck recordings is variable among subjects. From fig. 7, it is evident that this individual's PPV, while maximal over the ipsilateral neck (A and C), can even be detected in contralateral neck electrodes (E and G). On the other hand, the subject studied in fig. 6 demonstrates a PPV of lower amplitude and more restricted field. Desmedt and Cheron (1980) noted that in some patients, high cervical electrodes in the posterior midline record a 'small positive step' that precedes the cervical negativity (*see their* fig. 1, D–F). They suggested that this positivity represents volume conduction from the ascending volley. Comparison of their fig. 1 with our figs. 3 and 7 shows that this 'positive step' may actually be the return to baseline of a midline cervical negative deflection that occurs synchronously with the deflection corresponding to our N10, and by implication the PPV.

The interaction of PPV with other potentials recorded over the neck was noted by Yamada *et al.* (1980) who found that a lateralized negativity (their 'N11') appeared as a notch on the ascending limb of a later negative wave (their 'N13'). This interaction is critical if measurements are made using onset latencies. For example, in fig. 4, we might have assumed DCV onset to occur at the inflection indicated by the solid arrowheads. In view of contamination of the posterior midline electrodes by PPV in some individuals (figs. 7, 8), however, it is not easy to distinguish an inflection in the cervical negativity that marks the onset of DCV from one caused by the PPV returning to baseline. When seen in the posterior midline, PPV appears to be the most prominent in the upper cervical electrodes (figs. 7, 8). This may account for the large latency jump of the ostensible DCV onset from SC_2 to SC_1 in fig. 4. Similarly, it is likely that the onset of 'N13' in Desmedt and Cheron's fig. 1 (1980) is merely the return to baseline of the PPV recorded in the posterior midline.

The Dorsal Column Volley

Lesser *et al.* (1981) recorded intraoperatively following median nerve stimulation using electrodes positioned on the dorsal cord. They demonstrated a travelling wave which increased in latency from C7 to C3 and corresponded to conduction of the

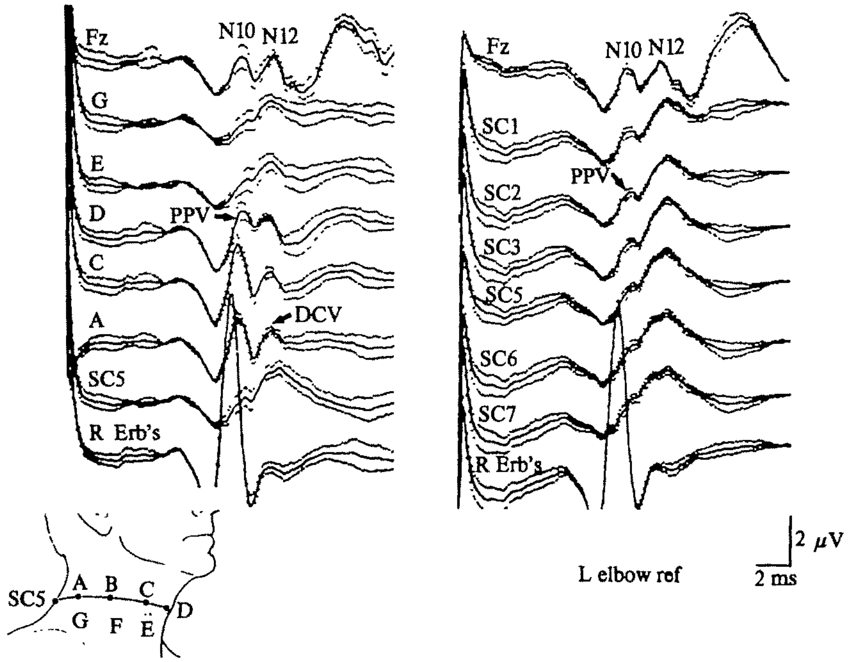

FIG. 7. SEP following right median nerve stimulation recorded from electrodes arranged in a ring about the neck (A) and vertically spaced along the posterior neck in the midline (B). In this individual, PPV is more widely distributed than in the individual illustrated in fig. 6, being present in the posterior midline, and even contralaterally.

afferent signal in the dorsal columns. We demonstrated that surface electrodes placed over the posterior neck also record a negative wave that increases in latency from C7 to C1 and presumably represents the dorsal column volley (fig. 4). Desmedt and Cheron (1980, 1981*a*), using a noncephalic reference, previously observed this phenomenon, as did Cracco (1973) using an earlobe reference. In contrast, authors who used an Fz reference (Matthews *et al.*, 1974; Jones, 1977), did not demonstrate a latency shift because far-field activity at Fz obscures input from the cervical electrodes (Desmedt and Cheron, 1980, 1981*a*).

Lueders *et al.* (1983) recorded from posterior neck electrodes referred to the shoulder and failed to observe a travelling wave that could be attributed to the dorsal column volley. They ascribed this to the 'almost complete obscuration' of the dorsal column volley by bony structures of the spinal canal which, they concluded, selectively attenuate the high frequency afferent volley but have relatively little effect on the slower postsynaptic potentials arising in the dorsal horn. From our studies it seems more likely that in some individuals, DCV is inapparent over the posterior neck because it is masked by the posterior negativity of the CERV N13/P13 potential. In such cases, it can be delineated by lateral neck electrodes where the CERV N13/P13 dipole (*see later*) is at its null point (fig. 8). In individuals where the PPV extends posteriorly (fig. 7), this peak too may be confused with the DCV.

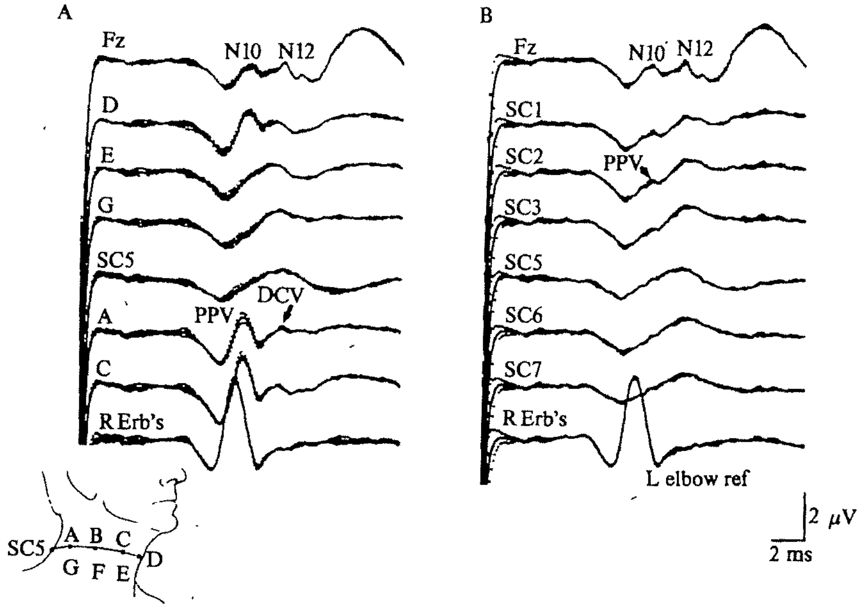

FIG. 8. SEP following right median nerve stimulation recorded from electrodes arranged in a ring about the neck (A) and vertically spaced along the posterior neck in the midline (B). In this individual, DCV cannot be distinguished from CERV N13 in the posterior midline but is evident in lateral neck electrodes. PPV is evident over the posterior midline in the upper cervical electrodes.

These considerations make it difficult to determine dorsal column conduction velocity using posterior cervical electrodes. Desmedt and Cheron (1980) calculated reasonable conduction velocities derived from sequential latency shifts of the apparent onset of the travelling cervical negativity. Their results may have been appropriate only fortuitously, however, since as already discussed, such measurements may be complicated by the interaction of DCV with other cervical potentials. For example, interaction of the DCV negative peak with the dorsally-recorded PPV or the later CERV N13 could distort DCV latency measurements in the following way. CERV N13 is diminished in amplitude over the upper cord (fig. 4; also Desmedt and Cheron, 1981*a*), and thus selective addition of the beginning of CERV N13 to DCV over the lower and midcervical cord would tend to cause an apparent delay of the peaks of these DCV negativities (but not more rostral ones) producing an erroneously small latency shift from lower to upper cervical levels.

The CERV N13/P13

We confirmed the studies of Desmedt and Cheron (1981*a*) and Lueders *et al.* (1983) that provide evidence for a fixed generator of near-field potentials in the cervical cord. Using both oesophageal and anterior cervical electrodes, Desmedt and Cheron (1981*a*) demonstrated a prevertebral stationary positivity, 'P13', over low to midneck levels that is coincident with a posterior negativity, 'N13'. Our CERV N13/P13 is undoubtedly identical. Desmedt and Cheron (1981*a*) suggested that this N13-P13 component is generated postsynaptically in the dorsal horn. Lueders *et al.* (1983) found a low frequency posterior cervical negativity (their 'N12') with similar latency and spatial characteristics that was also attributed to postsynaptic activity in dorsal grey matter. The CERV N13/P13 behaves as a dipole with maximal negativity posteriorly and maximal positivity anteriorly. It reverses phase with a null point over the lateral neck. Similar observations have been made experimentally in cats (Austin and McCouch, 1955; Coombs *et al.*, 1956; Fernandez de Molina and Gray, 1957) and monkeys (Austin and McCouch, 1955; Beall *et al.*, 1977). Direct recordings demonstrate one or more intramedullary potentials that reverse phase between dorsal and ventral grey matter. These are thought to arise from synaptic activity occurring on interneurons, motoneurons and second order sensory neurons.

The Far-field Potentials

It has been customary to regard the early scalp-recorded response following median nerve stimulation as a series of far-field positive waves (Trojaborg and Jørgensen, 1973; Matthews *et al.*, 1974; Cracco and Cracco, 1976; Jones, 1977; Kritevsky and Wiederholt, 1978; Arezzo *et al.*, 1979; Cracco, 1980; Desmedt and Cheron, 1980, 1981*a*, *b*; Wiederholt, 1980; Yamada *et al.*, 1980; Anziska and Cracco, 1981; Lueders *et al.*, 1983). The first, P9, corresponds to the arrival of the afferent volley at the axilla (Cracco, 1973; Cracco and Cracco, 1976; Jones, 1977;

Chiappa *et al.*, 1980; Desmedt and Cheron, 1980; Wiederholt, 1980). While Lueders *et al.* (1983) note the existence of subsequent negativities corresponding to our N10 and N12, they do not consider them in detail, asserting that 'The far-field potentials recorded from Fpz consist of three major positive deflections . . .'. Our results indicate that early scalp-recorded median SEP components after P9 include true negativities, N10 and N12. Figs. 1 and 2 clearly show that these are not merely passive returns to baseline following preceding positive deflections. Although unlabelled, the negative excursions above baseline of peaks corresponding to our N10 and N12 are readily seen in the illustrations of Lueders *et al.* (1983, *see* fig. 16).

We have shown that the scalp-recorded N10 coincides with the neck-recorded PPV, but exactly where along the course of the brachial plexus or cervical roots the N10 far-field is generated is not known. Lueders *et al.* (1983) commented that the scalp negativity following P9 and preceding their 'P11' had a latency similar but not necessarily identical to their cervical 'N10', which most probably corresponds to the PPV present over the posterior neck. We noted a similar variation in the exact relationship of N10 to the PPV, but found that N10 most often coincides with PPV latency measured at a superior thyroid electrode. It may actually occur before the PPV is recorded over SC_5 (fig. 7).

It should be emphasized that while PPV is a travelling wave, the latency shift from caudal to rostral electrodes in a vertical lateral neck array is variable from individual to individual, an observation most likely related to these electrodes being obliquely orientated with respect to the course of the brachial plexus in the neck. The latency of the PPV negativity recorded by each electrode in such a vertical array is determined by the part of the plexus best 'seen' by that electrode. This in turn relates to factors such as different electrical properties of intervening cervical structures and individual variations in neck geometry. Such considerations most likely account for a similarly variable latency shift between the PPV peak measured over the ipsilateral neck, SC_5 and the thyroid cartilage (figs. 6, 7, 8).

By measuring the velocity of the afferent volley in the peripheral nerve and extrapolating centrally, Desmedt and Cheron (1980) concluded that their 'P11' (the positive peak between our N10 and N12) coincided with the spinal entry of the afferent volley. In intraoperative recordings, Lueders *et al.* (1983) observed that the peak of the afferent volley at the C6 posterior root coincided with the 'P11' positivity at Fpz, and concluded that their 'P11' is generated in the dorsal rootlet. In fig. 17 from Lueders *et al.* (1983), this positivity is preceded by a large, unlabelled negativity which corresponds to our N10. It is difficult to determine, however, whether 'P11' is an actively generated potential as Lueders and associates suggest, or instead represents the return towards baseline of the N10 (which itself is probably superimposed upon the return to baseline of the preceding P9). We favour the latter possibility. The N12 latency coincides exactly with the arrival of the DCV at the SC_1 level. It is therefore likely that the generation of the N12 far-field potential is a presynaptic event occurring at or before termination of the sensory volley in the cuneate nucleus.

As Lueders *et al.* (1983) point out, there is no good explanation for the generation of scalp recorded far-field potentials. It is generally held that subcortical nuclei probably do not contribute significantly to far-field activity because their neuronal elements are not organized in a sufficiently regular array to provide for current flow outside their boundaries (Lorente de Nó, 1947*a*; Klee and Rall, 1977). On the other hand, the linearly orientated fibres of white matter tracts may be viewed as 'open field systems' that would be expected to generate far-field potentials (Arezzo *et al.*, 1979; Klee and Rall, 1977). It has been commonly assumed that since these potentials are recorded at the surface, beyond the termination of the active fibres, they must be of positive polarity (Arezzo *et al.*, 1979). This assumption is based upon either a theoretical model of an exploring electrode in a uniform volume conductor at a distance from the active neural element or an experimental model in which the recording electrode is located at a distance from the crushed end of nerve in a saline bath (Lorente de Nó, 1947*b*; Woodbury, 1965). These considerations are likely to be greatly oversimplified or even irrelevant for the genesis of evoked potentials. Robinson *et al.* (1965) have demonstrated the singular nonuniformity of brain conductive properties. We have shown that the scalp-recorded short latency far-field potentials following median nerve stimulation in man include two active negative deflections. Lueders *et al.* (1983) have recognized these same far-field negativities, and Tsuji *et al.* (1983) have described a far-field negative wave over the ipsilateral mastoid process accompanying wave III of the brainstem auditory evoked potential. Desmedt and Cheron (1981*b*) have reported that later components of the scalp-recorded median SEP include a large, widespread, far-field negativity (the N18), preceding a localized negativity over the contralateral primary sensory area (the N20).

These observations suggest that until the exact neural elements giving rise to particular components of the evoked potential waveform are known and details of geometry that affect current flow specified, it is unreasonable to assume *a priori* knowledge about scalp potential polarity. Model systems should be developed that more accurately reproduce the actual geometry and electrical properties of the human brain, skull and neck in relation to presumed neural generators.

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SYMPATHETIC ACTIVITY IN MAN AFTER SPINAL CORD INJURY

OUTFLOW TO SKIN BELOW THE LESION

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SUMMARY

Microelectrode recordings were made in peroneal skin nerve fascicles in 8 patients with functionally complete spinal cord lesions mainly at cervical levels. Spontaneous neural activity was sparse but deep breaths, abdominal pressure over the bladder and mechanical and electrical skin stimuli applied caudal to the spinal transection induced bursts of neural impulses after a latency of 0.5 to 1 s. The efferent discharges were conducted with a velocity of 0.75 m/s and were followed by cutaneous vasoconstriction and/or reduction of skin resistance. It is concluded that the neural bursts contained sympathetic impulses of spinal origin. No systematic changes of nerve activity were induced by changes of ambient temperature, suggesting that sympathetic thermoregulatory reflexes do not occur at spinal level in man. The vasoconstriction following a single sympathetic burst had a longer duration in the spinal patients than in normal subjects. The low level of spontaneous activity does not suggest permanent spinal sympathetic hyperactivity, but the prolonged episodes of vasoconstriction may contribute to attacks of high blood pressure in patients with spinal cord lesions.

INTRODUCTION

It is well established that spinal cord transection in man causes a major derangement in the sympathetic control of blood pressure and body temperature. In addition, many patients with such lesions experience attacks of 'autonomic hyperreflexia' with symptoms of paroxysmal hypertension, sweating, piloerection, pounding headache and anxiety that may be a serious clinical problem (Erickson, 1980). Much work has been undertaken on paraplegic and tetraplegic patients to study sympathetic function below the level of the lesion using sympathetic effector organ responses and neurohormone levels as markers of nerve activity (for references, *see* Frankel and Mathias, 1976). So far, however, direct observations are not available on sympathetic outflow from the functionally isolated spinal cord in man.

During the last decade a microelectrode recording technique has been used to study sympathetic activity in limb nerves of intact human subjects (for references, *see* Wallin, 1981). Such recordings have shown that sympathetic activity in skin

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nerves is made up by vasoconstrictor and sudomotor impulses which are discharged in spontaneously occurring irregular bursts. The main function of this activity is to participate in thermoregulation and at room temperature spontaneous activity in a relaxed subject is dominated by vasoconstrictor impulses (Hagbarth, *et al.*, 1972; Bini *et al.*, 1980*a*). Rapid deep breaths and various arousal stimuli evoke single reflex discharges containing a mixture of sudomotor and vasomotor impulses, and stimuli associated with emotional reactions (for example, mental arithmetic) lead to a more long-lasting outflow of both vasoconstrictor and sudomotor impulses. Simultaneous double nerve recordings show that the sympathetic discharges occur in parallel in nerves innervating the palm of the hand and the foot (Bini *et al.*, 1980*b*).

The present study was undertaken to investigate whether the microneurographic technique could also be used to record sympathetic outflow below the level of the lesion in spinal man. This was found to be the case and the present report describes results from skin nerve recordings in patients with functionally complete spinal cord lesions mainly at cervical level. Some of the findings have been reported in preliminary form (Stjernberg and Wallin, 1983).

METHODS

The clinical details of the patients are presented in Table 1. Experiments were made on 7 males and one female, aged 19 to 53 yrs, with traumatic spinal cord lesions, who gave their informed consent to the investigation. In one patient the lowest intact cord segment was T7; the others had cervical lesions with lowest intact segment at C5 to C8. In all patients there was complete absence of sensation and voluntary motor function below the level of the lesion and, as far as could be judged clinically, the transection of the cord was complete. All patients had moderately increased muscle tone and tendon jerks below the level of the lesion and sometimes they exhibited minor involuntary movements in the legs. One patient had clear symptoms of exaggerated autonomic reflexes such as attacks of pronounced sweating, flushing of the face, headache and a feeling of general discomfort. These symptoms were most common when the bladder had not been emptied for several hours. The other patients had only occasional minor episodes of sweating. Two patients had positive urinary cultures at the time of the

TABLE 1. CLINICAL DATA

Case no., sex, no. of recording	*Level of lesion*	*Patient's age at time of recording (yrs)*	*Age of lesion at recording (months)*	*Relevant medication (daily dosage)*
1, M I	C5	24	6	Diazepam 10 mg
II		24	7	Diazepam 10 mg
III		26	26	Baclofen 150 mg; diazepam 15 mg; phenytoin 100 mg
2, F	C6	23	4	0
3, M	C7	15	12	0
4, M	C7	30	60	Baclofen 20 mg
5, M I	C7	39	11	Diazepam 15 mg; baclofen 45 mg
II		40	14	Baclofen 45 mg
6, M I	C8	19	9	Carbamazepine 800 mg
II		19	10	0
III		21	29	0
7, M I	C8	53	9	Baclofen 225 mg; diazepam 5 mg
II		53	10	Baclofen 225 mg; diazepam 11 mg
8, M	T7	22	36	Baclofen 150 mg; oxazepam 45 mg; propantheline bromide 90 mg

experiments. None had an indwelling catheter. In 10 experiments the patients were on some form of medication (*see* Table 1), but not in 4 of the experiments. Successful microelectrode recordings were made from 18 skin fascicles in the peroneal nerve at the fibular head in 14 experiments. Peroneal nerve recordings were also made in 7 healthy control subjects, 5 men and 2 women, aged 25 to 43 yrs.

Recording Equipment

Insulated tungsten microelectrodes, with uninsulated tip diameters of a few μm, were used for the nerve recordings. A reference electrode of the same type but with a larger uninsulated tip was inserted subcutaneously about 2 cm from the recording electrode. The electrodes were connected to a differential preamplifier with a gain of 1000 and the nerve signal then amplified with an additional gain of 50. It was fed through a bandpass filter (band width 700 to 2000 Hz) and an amplitude discriminator to improve signal-to-noise ratio. An RC-integrating network (time constant 0.1 s) was used to obtain a mean voltage display of the nerve signal. During the recordings nerve activity was monitored with a storage oscilloscope (Tektronix 549) and a loudspeaker. The unfiltered and mean voltage neurograms were stored together with other variables on an 8-channel tape recorder (Sangamo Sabre VI). In the simultaneous recording from two sites in the same nerve, an additional identical recording and display system was used. Electronic interaction between the two recording systems was excluded by careful controls. The ECG was recorded by surface electrodes on the chest. Respiratory movements were recorded by a strain gauge attached around the chest with a rubber strap. In all experiments cutaneous vasomotor responses were monitored by a photoelectric pulse plethysmograph (van Gogh ILP-ZA) and in most cases skin resistance variations were recorded by a van Gogh galvanic skin reflex module type IGSR-ZA (a.c. coupled, rise time constant 0.35 s, decay time constant 3 s) with AgAgCl electrodes (Beckman). Sometimes effector responses were monitored on the dorsum of the foot within the innervation zone of the impaled peroneal fascicle but usually they were recorded on the plantar side of the hallux (plethysmograph) and the sole of the foot (skin resistance), that is, from the innervation zone of the tibial nerve. In some experiments an accelerometer was attached to the hallux on the same side as the recordings to detect foot movements. In other experiments surface or needle EMG was recorded with high gain from anterior compartment muscles in the lower leg.

Experimental Procedure

The subjects sat or lay in a comfortable position with the leg to be recorded from slightly flexed and supported by a vacuum cushion. Room temperature was 22 to 24° C. The experiments could last 2 to 3 h and to prevent development of pressure sores in the patients, bony areas were supported by soft pads. For technical reasons recordings were usually made from the less spastic leg. The nerve was localized with the aid of electrical stimuli delivered first *via* surface electrodes on the skin and then *via* the tungsten microelectrodes.

Recording technique and criteria for identifying sympathetic activity in healthy subjects have been described previously (Hagbarth *et al.*, 1972; Bini *et al.*, 1980*a*). As the patients had complete sensory loss in the legs their subjective sensations could not be used when identifying the impaled fascicles. For skin nerve fascicles in the patients the following criteria were used: (1) afferent mechanoreceptive impulses were evoked by touching the skin and (2) muscle taps and stretches did not give rise to afferent activity. Corresponding criteria for muscle nerve fascicles were: (1) weak electrical stimuli delivered through the recording electrode evoked muscle twitches and (2) tapping on the muscle belly or passive stretching of the muscle gave rise to afferent mechanoreceptive activity.

When a skin fascicle had been impaled and identified, small electrode adjustments were made until the activity to be described was encountered. Since spontaneous activity was sparse this involved application of various stimuli (*see* Results) after each electrode movement. To find and maintain a good recording position was more difficult than in healthy subjects because of a tendency to involuntary leg movements. Such reflexes were often brought about by electrode movements and were especially common if the electrode tip was localized inside the fascicle. On some occasions physiotherapy was given before the experiment to minimize spasticity and facilitate recording.

Manoeuvres

In attempts to induce neural activity the following tests were made: (1) firm manual pressure on the abdomen over the bladder ('bladder pressure'), (2) cutaneous electrical stimuli (0.2 ms duration and up to 150 V amplitude) and (3) skin pinches. In 4 experiments on patients with spinal cord lesions environmental temperature was varied. Patients were then lying in shorts inside a box used for hypothermic surgery (Auto HypoTherm, Super Automatic Neurosurgery XM, Heljestrand, Stockholm). Nerve activity at rest and responses to bladder pressure (delivered through an opening in the cover) were recorded at a box temperature of 22 to 24° C and then temperature in the box was either gradually increased or decreased. To check that the recording site was maintained occasional bladder pressures were made. The tolerance of the patients to temperature changes varied and the temperature range could not be standardized. Details of temperatures and duration of changes are given in Table 2. In addition to the pulse plethysmogram and skin resistance, central core temperature was monitored by a thermocouple in the external auditory canal close to the ear drum.

Analysis

For analysis the mean voltage neurogram and other analog signals were displayed on an ink jet recorder (Mingograph 800, Siemens-Elema Ltd., Stockholm) with a paper speed of 5 mm/s. Latency measurements were made manually with 0.5 mm accuracy from a chart recorded with a paper speed of 50 mm/s.

RESULTS

Spontaneous Activity

In contrast to findings in intact man, spontaneous neural activity was sparse in all patients with spinal cord transection and spontaneous bursts clearly seen in the mean voltage neurogram were extremely rare (fig. 1). To quantify the difference, spontaneous neural bursts were counted in the mean voltage neurogram during a 3 min rest period in 4 healthy and 4 tetraplegic subjects. In the normal subjects bursts were of sympathetic origin (according to criteria described previously (Hagbarth *et al.*, 1972; Delius *et al.*, 1972)) and in the tetraplegic patients only such electrode sites were accepted in which neural reflex bursts could be evoked by the manoeuvres described below. The total number of spontaneous bursts in all subjects was 160 in the normal group (21 to 68 in each subject) and 1 in the tetraplegic group. Even if synchronized neural discharges were rare, in some patients occasional weak

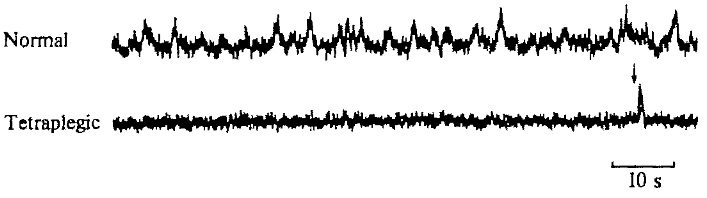

FIG. 1. Mean voltage neurograms from peroneal skin nerve fascicle in a normal subject and a tetraplegic patient (C6 lesion) at rest. Note frequent sympathetic bursts in the neurogram from the normal subject and only a single reflex burst induced by pressure over the bladder (*arrow*) in the tetraplegic patient.

discharges or random spike-like potentials occurred in the original neurogram which were difficult to discern in the mean voltage neurogram. Often it was difficult to separate this activity from artefacts but sometimes the discharges were followed by plethysmographic signs of vasoconstriction (*see below*), suggesting that they were of neural origin.

Induced Activity

Several manoeuvres elicited multiunit neural discharges. By far the most efficient stimulus was bladder pressure, which in all patients evoked well defined responses in the mean voltage neurogram. Both onset and release of pressure could evoke single bursts of impulses (fig. 2A). 'On-bursts' were usually stronger and more frequent and occurred with 41 of 50 stimulations whereas 'off-bursts' occurred only in 26 of the tests. The more rapid the stimulus the easier it was to elicit a response. The latency from start of pressure to the beginning of the 'on-burst' was approximately 0.5 to 1.0 s and the duration of the burst was about 1 s. Sometimes occasional poorly defined bursts were seen between the 'on' and the 'off-burst' but, as a rule, there was no discernible synchronized neural activity during maintained bladder pressure. However, in a few instances during a recording with good signal-to-noise ratio,

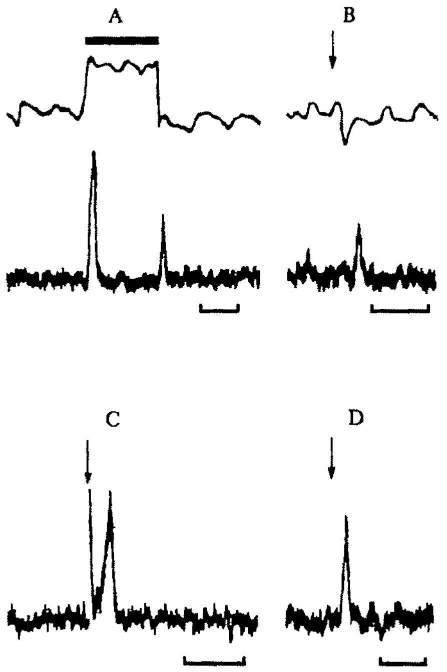

FIG. 2. Peroneal mean voltage neural bursts evoked by A, pressure over the bladder. B, a deep breath. C, a short train of electrical stimuli delivered *via* intracutaneous needle electrodes to the abdominal skin over the bladder. D, and a skin pinch applied over the bladder in patients with cervical spinal cord transection. Upper traces in A and B: respiratory movements (inspiration upwards). Manoeuvres indicated by horizontal bar (A) and arrows (B–D). Time calibration 5 s.

pressure over the bladder was associated with desynchronized impulse activity, readily observed in the discriminated neurogram but more difficult to see in the mean voltage neurogram. In the example shown in fig. 3 desynchronized firing started during the latter half of the manoeuvre (about 15 s after the 'on-burst') and continued approximately 40 s after release of pressure. In another case there was no desynchronized impulse activity during the application of pressure over the bladder, but it started 5 s after release of pressure and lasted approximately 30 s.

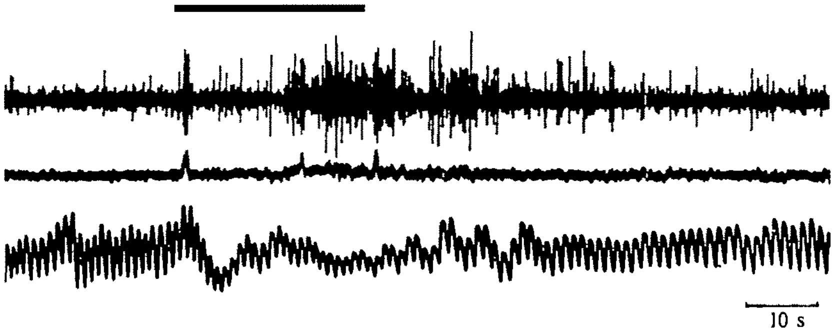

FIG. 3. Desynchronized peroneal neural activity (best seen in discriminated neurogram, *upper tracing*) evoked in conjunction with application of pressure over the bladder (*horizontal bar*). 'On' and 'off-bursts' are best seen in the mean voltage neurogram (*middle tracing*). Note similarity between durations of neural discharge and plethysmographic pulse amplitude reduction (recorded from plantar side of the hallux, *lowest tracing*).

In intact man mechanical and electrical skin stimuli usually evoke sympathetic reflex responses which occur after a latency of less than 1 s (Hagbarth *et al.*, 1972). The same type of stimuli applied below the level of the lesion could evoke neural bursts of similar appearance in patients with spinal cord transection. In patients, however, stimuli had to be much stronger than in normal subjects. For example, an unexpected light skin touch or a single electrical skin stimulus perceived as a skin tap, which often evoke strong reflex discharges in intact subjects, did not give rise to a response in the patients, independent of whether the stimulus was unexpected or not. However, a strong skin pinch (fig. 2D) or a train of 3 to 10 impulses at 150 V (usually perceived as painful in intact subjects) applied to the abdominal wall (fig. 2C) or the contralateral leg (fig. 6E) could evoke single neural bursts of similar appearance and latency as in normal subjects. When applied above the level of the spinal lesion mechanical and electrical skin stimuli never evoked neural responses. Similarly reflex discharges were never elicited by loud sounds. On 6 occasions subjects were asked to perform deep inspirations but due to the high level of the spinal lesions the effort usually resulted only in a small gasp. Following three of these a neural burst was elicited (fig. 2B).

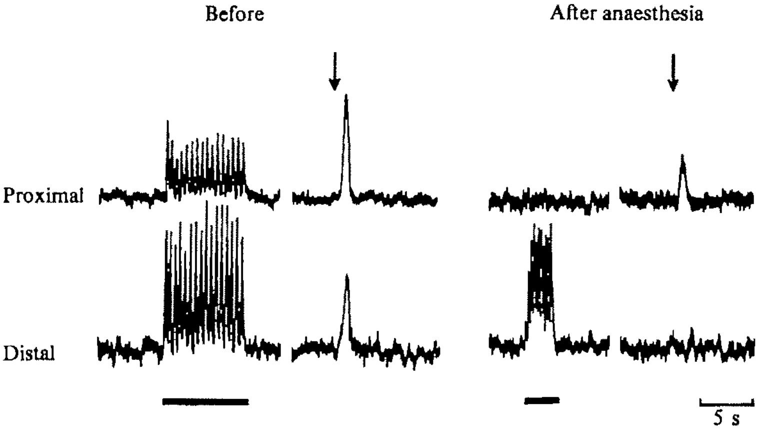

FIG. 4. Effects of local anaesthetic block on mean voltage neurograms recorded simultaneously at two sites in the right peroneal nerve in a patient with spinal cord transection at the C6 level. Before anaesthesia (*left*) neural activity was recorded at both electrode sites in response to repeated cutaneous touch stimuli on the foot (*horizontal bar*) and in response to application of pressure over the bladder (*arrow*). After anaesthesia (*right*) responses to touch stimuli were recorded only at the distal, and responses to bladder pressure only at the proximal electrode.

Evidence on the Origin of the Activity

Nerve block with local anaesthetic. This was tested in 2 patients and the results showed that the activity was efferent. In one case 10 ml prilocain 10 mg/ml (Citanest) was injected around the peroneal nerve 5 cm distal to the recording site. Neural responses to bladder pressure were unaffected whereas afferent responses to touch stimuli within the receptive field on the foot no longer could be recorded. In another patient simultaneous recordings were made from two sites in the same peroneal nerve to determine conduction velocity (*see below*). As shown in fig. 4 pressure over the bladder (arrow) and touch stimuli (horizontal bar) within the receptive field on the foot evoked neural responses at both recording sites. At the end of the experiment prilocain was injected between the recording electrodes. After the anaesthesia, activity evoked by stimuli on the foot could be recorded only from the distal recording site and activity evoked by bladder pressure only from the proximal recording site.

Conduction velocity determination. To determine conduction velocity, simultaneous recordings were made in one patient from two sites 6.7 cm apart in the peroneal nerve. Presumably the same nerve fascicle was impaled by both electrodes since the receptive fields were almost identical on the dorsum of the foot. When bursts occurred they were almost always recorded at both electrode sites (fig. 5A), first at the proximal electrode and about 0.1 s later at the distal electrode (fig. 5B). The histogram in fig. 5C shows the distribution of conduction times between the two recording sites for 43 bursts. Using the mean latency of 0.089 s, conduction velocity was calculated to be 0.75 m/s.

Relationship between nerve activity and cutaneous sympathetic effector responses. When plethysmographic and skin resistance responses were recorded within the innervation zone of the impaled nerve fascicle neural bursts were regularly followed by signs of vasoconstriction and/or skin resistance reduction (fig. 6A). In most instances findings were similar if effector responses were recorded from the plantar side of the foot, that is, *peroneal* neural bursts were succeeded by one or both types of effector responses also within the innervation zone of the *tibial* nerve (fig. 6B–D). Sometimes, however, plantar effector responses occurred which were not preceded by peroneal neural activity. Examples of such skin resistance and vasomotor responses are illustrated in fig. 6C and D, respectively. In one experiment the reverse situation occurred, that is, cutaneous electrical stimuli in the contralateral leg gave rise to single bursts of impulses in the peroneal nerve, some of which were not followed by plantar effector responses (fig. 6E). Latencies between the beginning of neural bursts and the start of effector responses were 2 to 5 s for vasomotor and 2 to 4 s for skin resistance responses.

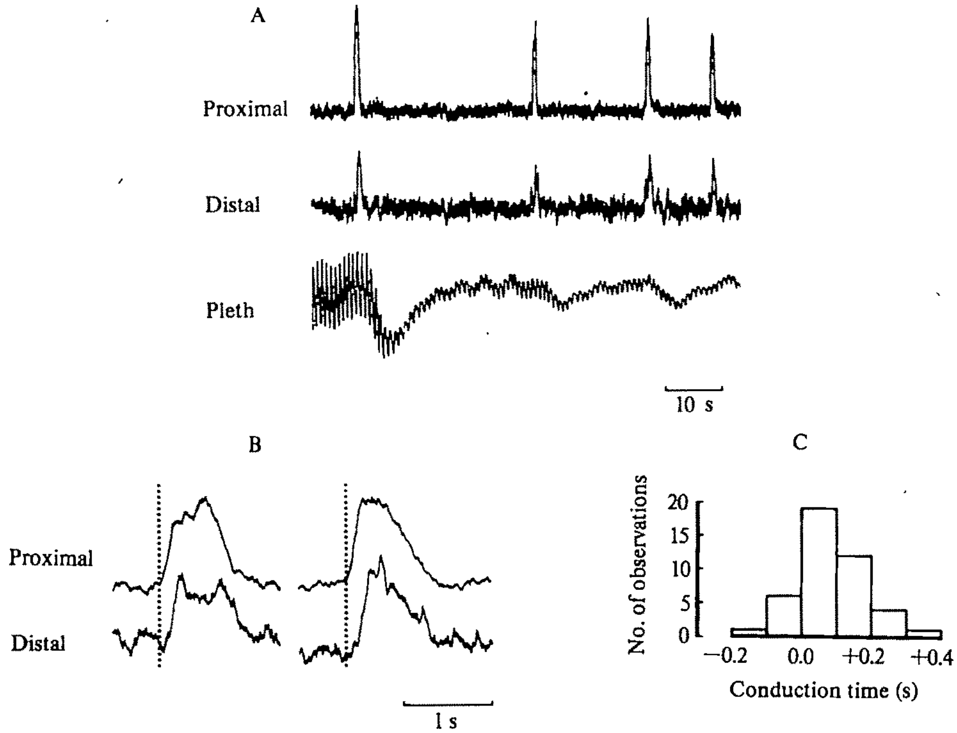

FIG. 5. A, mean voltage neural activity recorded simultaneously at two sites 6.7 cm apart in the right peroneal nerve (same experiment as in fig. 3). Neural bursts were evoked by repeated applications of pressure over the bladder. A pulse plethysmogram (Pleth) was recorded from the plantar side of the hallux. B, traces showing the time relationship between neural bursts recorded at the two sites. C, histogram of burst conduction times (n = 43) between proximal and distal recording electrodes from measurements taken at start of bursts in mean voltage records as indicated by dotted lines in B. Negative sign indicate bursts first seen at the distal electrode. Mean conduction time 0.089 s.

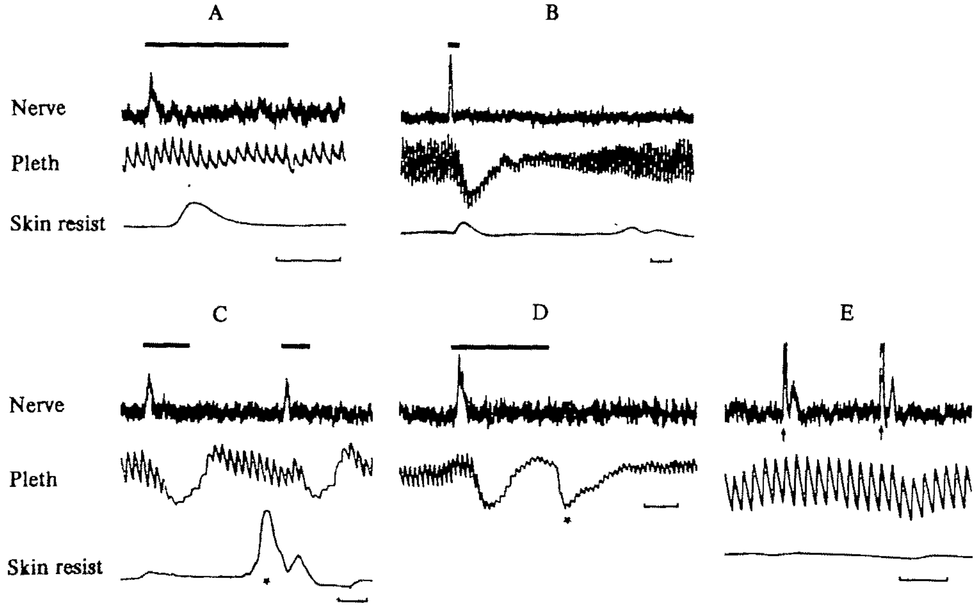

FIG. 6. Relationship between neural bursts evoked by pressure over the bladder (*horizontal bars*) or electrical skin stimulation of contralateral leg (*arrows*) and cutaneous effector responses. All mean voltage neurograms are from the peroneal nerve and effector organ recordings from the innervation zone of the nerve on the dorsum of the foot in A and from the plantar side of the foot in B–E. Reduction of skin resistance is indicated by upward deflection. Note differences in duration of plethysmographic responses (Pleth) in B and C and absence of peroneal neural bursts preceding skin resistance response in C (*asterisk*) and plethysmographic response in D (*asterisk*). E shows peroneal bursts in response to cutaneous electrical stimuli which were not followed by plantar effector responses. Time calibration 5 s.

The duration of the episodes of vasoconstriction varied considerably but compared with intact man the duration was often prolonged in the patients. The time from the beginning of a single induced peroneal neural burst to the end of corresponding vasoconstriction on the plantar side of the hallux was measured in 4 patients (24 observations) and 5 normal subjects (59 observations). The duration of the vasoconstrictor responses were calculated in the following way. The mean amplitude of the last five pulses in the plethysmogram before the stimulus was determined and an amplitude reduction of 50 per cent or more was accepted as a response to the induced burst. Vasoconstriction was considered terminated when pulse amplitudes had returned to 90 per cent of the prestimulus amplitude. In the patients the duration of the episodes of vasoconstriction was 32.1 ± 20.1 s (mean ± SD), range 10 to 103 s, and in the normal subjects 10.6 ± 5.0, range 4 to 23 s (significant difference, $P < 0.01$). In a few instances with long duration effector responses, the peroneal neural burst was succeeded by desynchronized impulse activity (fig. 3). This type of prolonged neural activity was an exception, however, and in most cases with long episodes of vasoconstriction there was only a well defined neural burst and no after-discharge.

To support the view that vasoconstrictor responses were induced by neural impulses and not by humoral agents, two types of experiment were performed. (1) In 2 patients with C5 lesions vasomotor responses to pressure over the bladder were monitored simultaneously from the palmar side of the index finger of both left and right hands. In the control situation each stimulus usually induced vasomotor responses on both sides but after blocking one median nerve with local anaesthetic (prilocain 10 mg/ml) at the wrist, vasomotor responses were obtained only from the nonanaesthetized side. (2) In one patient with a T7 lesion, pulse plethysmograms were monitored simultaneously in one hand and one foot while electrical skin stimuli were applied either above or below the level of the lesion. When stimuli were applied above the level of the lesion there was vasoconstriction only in the hand and when stimuli were applied below the level of the lesion responses were obtained only in the foot.

Changes of Ambient Temperature

In 4 patients nerve recordings were made while ambient temperature was varied. In 1 experiment ambient temperature was only lowered and in 3 experiments both lowered and increased compared with normal room temperature. The temperature changes and corresponding effects on central core temperature are detailed in Table 2. In 3 patients neural background activity and plethysmographic pulse amplitudes were unchanged during the temperature variations and there was no obvious difference between reflex bursts induced at different ambient temperatures. In the fourth patient two 1 to 2 min periods with signs of vasoconstriction were observed.

TABLE 2. VARIATIONS OF EXTERNAL TEMPERATURE IN TETRAPLEGIC PATIENTS

Case	*Temperature variation*	*Time from start of experiment (min)*	*Box temperature (° C)*	*Ear temperature (° C)*
1	Cooling	0	23.8	35.8
	Warming	17	8.6	34.5
		70	42.5	35.1
3	Cooling	0	22.7	35.5
	Warming	20	9.2	33.1
		36	24.4	33.5
4	Cooling	0	27.1	35.7
	Warming	21	15.7	33.6
	Cooling	56	36.2	34.3
		60	25.7	—
6	Warming	0	23.6	35.7
	Cooling	23	33.9	35.2
		83	19.2	34.9

Temperatures given from start and end of experiment and when turning from cooling to warming (or *vice versa*).

One period occurred when ambient temperature was below and one when it was above normal room temperature (but below body temperature) and during both periods ear temperature was below the initial level. In this patient there were already some random weak spontaneous discharges in the control situation and the amount of such activity increased slightly during the periods of vasoconstriction. The change was small, however, and in the mean voltage neurogram only a few small deflections were seen. We did not study systematically the duration of vasoconstrictor responses to bladder pressure at different ambient temperatures. However, even if it may be a coincidence ($0.05 < P < 0.1$) it is worthy of notice that durations usually were longer during cooling (mean ± SD = 90.6 ± 55.8, n = 8) than in the control situation (47.4 ± 22.1, n = 6).

Muscle Spasms

One experimental difficulty was involuntary leg movement which was most common towards the end of a recording session and often dislodged the recording electrode. These muscle spasms had the character of flexor reflexes and could occur spontaneously but most commonly they were induced either by external stimuli to the skin below the level of the lesion or when the position of the intraneural electrode was adjusted. The strength of the spasms varied from small toe movements to strong flexions of the whole limb. In 2 subjects repeated small toe extensions occurred fairly regularly with intervals of 15 to 30 s during several minutes without dislodging the intraneural electrode. These muscle contractions were associated with discharges in the neurograms with durations of 3 to 4 s. Fig. 7 illustrates that the movements usually caused artefacts in the plethysmogram and in the skin resistance record followed by clear signs of vasoconstriction recorded from the plantar side of the big toe.

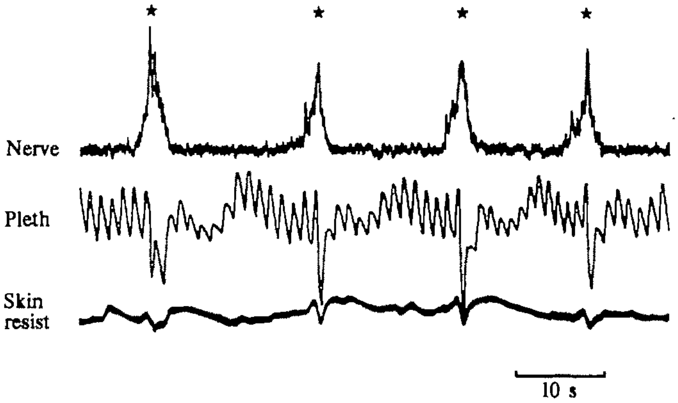

FIG. 7. Discharges in peroneal mean voltage neurogram (*asterisks*) evoked in association with spontaneous toe movements. Note artefacts at each movement in the plethysmogram (Pleth) and skin resistance record (both recorded from the plantar side of the foot), followed by reductions of pulse amplitudes in the plethysmogram.

DISCUSSION

The Origin of the Activity

During experiments special care was taken to exclude mechanical artefact as the source of the discharges in the neurogram described above. To detect such artefacts, recordings were made of foot movements and EMG from anterior compartment muscles. In addition the pulse plethysmograph proved to be a sensitive detector of toe movements (*see* fig. 7). Those neural bursts which were evoked without signs of concomitant EMG activity and foot movement consisted of efferent impulses with a conduction velocity of less than 1 m/s. They were succeeded by cutaneous vasoconstriction and/or skin resistance reduction after a latency of a few seconds. These observations strongly indicate that the bursts were of sympathetic origin and composed of vasoconstrictor and/or sudomotor impulses. Careful clinical examination of all patients gave no indication that the spinal lesions were incomplete. Available methods to judge the extent of a spinal transection can only demonstrate the incompleteness of the lesion but never prove its completeness. The characteristics of the sympathetic activity, however, were similar in all patients and differed from those of the activity found in normal man. Also, sympathetic bursts were induced by stimuli below but never above the level of the lesion. Therefore, even if supraspinal influences cannot be entirely excluded, there is no doubt that the sympathetic activity was mainly of spinal origin.

One main difference from the findings in normal man was the virtual absence of spontaneous activity in spinal patients. This suggests that most spontaneous sympathetic discharges in intact man are dependent on excitatory supraspinal influences. In a previous study, spontaneous sympathetic discharges to the foot and the palm of the hand were found to occur in synchrony and this was also taken as an indication of strong supraspinal excitatory influence on spinal sympathetic neurons (Bini *et al.*, 1980*b*). The lack of spontaneous sympathetic activity in spinal man was similar to findings in intact man under light to moderate general anaesthesia where spontaneously occurring discharges were absent, but where skin pinches and other sensory stimuli could still evoke sympathetic reflex responses in skin nerves (Wallin and Kõnig, 1976).

In tetraplegic patients cutaneous stimuli applied below the level of the lesion evoked sympathetic reflex discharges of similar appearance and with similar latency as those seen in skin nerve recordings in intact man (Hagbarth *et al.*, 1972), but to evoke responses in the patients much stronger stimuli were required than in normal subjects. This may indicate that in normal man these reflexes are also of spinal origin but that they are easier to elicit than in the patients because supraspinal facilitation is present. We cannot exclude, however, that in the patients a supraspinal low threshold reflex component is lost and that this explains why stronger stimuli are required to evoke reflex responses. One might also argue that the low spontaneous activity and the strong stimuli needed to induce neural bursts in spinal man could be an effect of medication similar to that observed during general anaesthesia.

Although pharmacological effects on spinal sympathetic neurons may have been present in some experiments the similarity of the responses, whether or not patients were on drugs, indicates that this was not the main reason.

Relationship between Sympathetic and Skeletomotor Activation

Sometimes spontaneous muscle spasms in the foot produced movement artefacts both in the neurogram and the plethysmographic record followed by clear plethysmographic evidence of cutaneous vasoconstriction (fig. 7). Presumably therefore the discharges in the neurogram (in addition to movement artefacts) also contained sympathetic impulses which were activated in parallel with the skeletomotor impulses. Other evidence of coupled excitation of sympathetic and skeletomotor neurons in spinal man were reported by Corbett *et al.* (1971*a*) who showed that spontaneous and induced muscle spasms were associated with blood pressure elevation and reduction of calf and hand blood flow. Corbett *et al.* tacitly assumed that sympathetic activation was a reflex effect, secondary to muscle contraction. In our subjects the delay between the start of the discharges in the neurogram and the beginning of the pulse amplitude reduction in the plethysmogram was difficult to determine exactly because of the movement artefact, but as far as can be judged it was not prolonged compared with vasoconstrictor responses without muscle contraction. Thus the possibility exists that rather than being cause and effect, the spontaneous discharges in skeletomotor and sympathetic neurons occur simultaneously as a consequence of a generalized increase of spinal excitability.

Relationship between Sympathetic Activity and Effector Responses

Since sympathetic bursts could be followed by vasoconstriction and skin resistance reduction it is likely that both vasoconstrictor and sudomotor impulses were recorded. Judging from the pattern of effector responses the sympathetic bursts could contain either vasoconstrictor or sudomotor or both types of impulses. This is in agreement with findings in subjects with intact spinal cords where vasoconstrictor and sudomotor neurons may be activated either selectively or in parallel (Bini *et al.*, 1980*a*).

In subjects with an intact spinal cord, both spontaneous sympathetic bursts and bursts evoked by deep breaths and various arousal stimuli regularly occur synchronously with similar strengths in nerves supplying the palm of the hand and the foot (Bini *et al.*, 1980*b*). Similarly, vasoconstrictor and skin resistance responses also occur in parallel in the hands and feet (Burton, 1939; Sourek, 1965; Fuhrer, 1971). On the other hand, in the present recordings from patients with spinal cord lesions it was sometimes found that strong effector responses occurred within the innervation zone of the tibial nerve (fig. 6C, D) without corresponding sympathetic discharges in the peroneal nerve. In addition, examples were seen in which peroneal reflex bursts were not followed by plantar effector responses. This agrees with the results of Fuhrer (1971), who reported that electrical stimulation of the tibial nerve in one leg in patients with cervical spinal cord lesions gave rise to reflex changes of skin conductance which only rarely were synchronous in all four limbs. Thus, although anatomically the intraspinal pathways must be intact (since widespread responses often did occur), cutaneous sympathetic reflex discharges have a more variable distribution in spinal than in intact man. This may be due to asynchronous fluctuations of the excitability level of different parts of the spinal cutaneous sympathetic neuron pool.

The reason for the prolonged vasoconstrictor responses in patients with spinal cord lesions is unclear. One possibility is that the initial synchronized sympathetic burst was followed by a slowly decreasing desynchronized after-discharge of the type shown in fig. 3. Such neural responses were uncommon, but effector recordings from the innervation zone of the impaled fascicle are necessary to decide how often such a mechanism may explain the long duration of the vasoconstriction. A second possibility is that the manoeuvre initiated not only a skin sympathetic discharge but also a release of cathecholamines from the adrenal medulla which would prolong the neurally mediated vasoconstriction. The findings that local anaesthesia of the nerve eliminated the vasoconstrictor responses and that stimuli applied below the level of the lesion did not induce vasoconstriction above the level of the lesion argues against this explanation. A third possibility is that in the patients, cutaneous vessels are hypersensitive to the transmitter released by the neural impulses and therefore respond in an abnormally protracted manner. Previous findings of an increased sensitivity in tetraplegics to the intravenous infusion of noradrenaline (Mathias *et al.*, 1976) would be compatible with this possibility.

It is of interest to consider the present findings in relation to possible mechanisms underlying the attacks of autonomic hyperreflexia sometimes seen in tetraplegics. Since there was less spontaneous activity and since stronger cutaneous stimuli were needed to evoke sympathetic reflexes in our patients than in normal subjects, there is no permanent hyperactivity of spinal cutaneous sympathetic neurons in tetraplegic patients. We have, however, seen episodes of spontaneous muscle contractions coupled with cutaneous vasoconstriction and also signs of a varying degree of synchrony between sympathetic discharges in different nerves which suggest spontaneous fluctuations of excitability in the spinal sympathetic neuron pool. This, together with the tendency for prolonged vasoconstrictor responses, could be of importance when episodes of 'autonomic hyperreflexia' are elicited. Once an attack is triggered another contributing factor is the absence of protective baroreflexes which in normal subjects would counteract the blood pressure increase resulting from the vasoconstriction.

The Experimental Manoeuvres

In normal subjects, both recordings of effector organ responses and sympathetic nerve activity show that rapid deep inspirations, skin pinches and electrical skin stimulation give rise to reflex vasoconstriction in the skin and sweating (Hagbarth *et al.*, 1972; Bini *et al.*, 1980*a*). Previous recordings of blood flow and skin resistance have shown that similar reflex responses are present also below the level of the lesion in patients with spinal cord transection (Gilliatt *et al.*, 1948; Fuhrer, 1971; Corbett, *et al.*, 1971*b*). The present results confirm that the effects are due to spinal sympathetic reflexes.

Several previous studies have shown that bladder filling and increase of intravesical pressure result in sweating, skin vasoconstriction and blood pressure increases (Head and Riddoch, 1917; Guttman and Whitteridge, 1947; Cunningham *et al.*, 1953). Furthermore, Corbett *et al.* (1971*a*) found that bladder percussion induced vasoconstriction even when intravesical pressure did not increase. In the present study the stimuli were short periods of firm pressure against the lower part of the abdomen in the region of the bladder and the results provide direct confirmation of previous suppositions that the effects are due to sympathetic reflex activation. Since electrical stimulation and pinching of the abdominal skin over the bladder could also evoke sympathetic bursts it is probable that the reflex effects of bladder percussion or pressure against the abdomen are evoked from receptors both in the abdominal wall and in the bladder. This may partly explain why such stimuli are particularly efficient in evoking sympathetic reflex effects.

Spinal thermoregulatory reflexes have been demonstrated in animals (Simon, 1974), but it is unclear whether they also exist in man. Evidence for and against this possibility has been reviewed by Johnson and Spalding (1974) and Johnson (1976). Our finding that cooling reduced ear temperatures 1 to 2° C without systematic changes of sympathetic outflow are against the presence of spinal sympathetic thermoregulatory reflexes of functional importance. In this connection it is of interest that vasoconstriction induced by pressure over the bladder was usually more prolonged during body cooling. If this can be confirmed it may possibly indicate an increased temperature sensitivity of cutaneous vessels which could explain, at least partly, previous findings of increased vasoconstriction during cooling in patients with spinal cord transection (Randall *et al.*, 1966).

ACKNOWLEDGEMENTS

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NEUROLINGUISTIC STATUS AND LOCALIZATION OF LESION IN APHASIC PATIENTS WITH EXCLUSIVELY CONSONANT-VOWEL RECURRING UTTERANCES[1]

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SUMMARY

Eight patients are presented whose speech production consisted exclusively of one and the same recurring consonant-vowel (CV) syllable, similar to Broca's first patient Leborgne ('Tan-tan'). Their neurolinguistic, aphasiological and localizational status was examined and compared with 32 patients with standard global aphasia and 15 with Broca's aphasia.

Patients with exclusively CV speech production represent a variety of global aphasia, characterized by fluency of output and the preservation of some prosody. Localization of the CT lesion did not distinguish between the nonstandard fluent global aphasics described here and the well-known standard nonfluent global aphasics. The individual lesions in both subgroups show great variability in size and localization, which is not recognized in the usual cumulative representations of CT lesions.

INTRODUCTION

In one of his papers 'On affection of speech from disease of the brain' Jackson (1879–1880) described a variety of stereotypical language production which he called 'recurring utterances'. He divided these into four classes, namely, jargon (e.g. 'yabby' or 'watty'), meaningful words (e.g. 'man' or 'awful'), short stock phrases (e.g. 'yes, but you know', or 'oh, my God'), and the particles 'yes' or 'no', alone or 'both of these words'.

Jackson maintained that these recurring utterances had no propositional value. He did not comment on these patients' ability to comprehend, nor on other language modalities, such as repetition, reading and writing. It is curious that Jackson did not mention an even more restricted class of recurring utterances, where the patients produce exclusively CV syllables, such as dada, didi, dodo, mama, without being

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aware of this extreme limitation of output. This is the language production found in Paul Broca's (1861*a*) first patient Leborgne, who was limited to saying 'tan-tan', 'an' being the graphemic rendering of the French nasalized vowel /ã/. It is even more curious that most textbooks on aphasiology or neuropsychology do not mention this interesting aphasic phenomenon, with the exception of Hécaen and Albert (1978) who stress that 'these sounds may be strung together with meaningful modulation or intonation', that is, that they would have some propositional intention, expressed by suprasegmental features.

This paper reports the findings in 8 patients who produced one and the same CV syllable, the most primitive form of recurring utterances, and attempts to answer the following questions. (1) What is their neurolinguistic status? Which language modalities are disturbed and which ones are retained? (2) What is their aphasiological status? Do they belong to one of the standard or nonstandard syndromes of aphasia? (3) Where is the underlying brain lesion located?

PATIENTS AND METHODS

Sample characteristics are given in Table 1. The second column lists the recurring utterance produced by each patient. Speech production consisted exclusively of strings of one and the same CV cluster, in which the consonant was always a dental plosive or a nasal, except in the presence of dysarthria, where it could also be a fricative or a liquid, as in Cases 3, 4 and 7. The concomitant dysarthria in these patients, which results from defective motor control of the articulatory organs, explains the variation in consonant production.

Table 1 also gives the intervals between the date of onset and of the Aachen Aphasia Test (AAT) and CT examinations. The AAT is a standardized neurolinguistically conceived psychometric aphasia test developed in our unit for German speaking patients (Huber *et al.*, 1980; Willmes *et al.*, 1980; Weniger *et al.*, 1981; Willmes *et al.*, 1983). In addition to ratings of spontaneous speech, it includes the following subtests: Token Test, Repetition, Written Language, Naming and Comprehension. The aphasic syndrome, based on spontaneous speech and performance on the five subtests, was established not earlier than one month postonset. Recovery data were available on the basis of retesting for Cases 1, 3, 5 and 6 (*see* Table 5).

Besides the clinical classification on the basis of the test results, the data for each patient were subjected to an automatic classification procedure (ALLOC). ALLOC (Habbema *et al.*, 1974) is a non-

TABLE 1. SAMPLE CHARACTERISTICS OF PATIENTS WITH CV RECURRING UTTERANCES*

Case	*CV*	*Sex*	*Age (yrs) at onset*	*Interval (months) Onset/AAT***	*Interval (months) Onset/CT*	*Clinical classification*	*ALLOC*** classification*
1	Mä	M	73	1	16	Global	100% global
2	Ta	M	67	10	10	Global	100% global
3	An/l	F	68	1	17	Global	100% global
4	Od/r	F	70	35	35	Global	100% global
5	Do	M	51	1	16	Global	100% global
6	Di	M	61	1	20	Global	100% global
7	S/Na	M	53	22	29	Global	100% global
8	Ma	M	67	3	1	Global	100% global

* Aetiology was acute ischaemic infarction in all cases with no instances of recurrent infarctions. All patients were right-handed and had a right hemiparesis. ** Aachen Aphasia Test (*see text*). *** Automatic classification procedure (*see text*).

parametric discriminant analysis program which is used in our unit for the allocation of patients to one of the standard aphasic syndromes on the basis of their test results. The program has been constructed by means of a learning sample of 120 aphasic patients, 30 of each major syndrome, 30 right brain-damaged patients and 30 control patients without brain damage.

The aphasiological and lesion data of the 8 patients with CV speech production (CV patients) were compared with two other groups of aphasic patients, 32 patients with standard global aphasia and 15 with Broca's aphasia. Sample characteristics are given in Table 2.

For CT scan evaluation we selected the latest scan available postonset. Evaluation was undertaken according to a standardized method (Blunk *et al.*, 1981). A patient's lesion was mapped onto 5 grids, each corresponding to a CT slice. This procedure made it possible to construct coordinate matrices, on the basis of which further computation could be performed. The individual lesion information stored as 1/0 entries for each coordinate point could be used in absolute and relative frequency counts for selected groups of patients as well as for defined anatomical areas. For this study, the frequency counts of 1/0 entries were used for the patient groups standard global aphasia *versus* CV patients to determine the smallest cumulative lesion for each group. Since no lesion point was covered by all of the patients of one group, a cut-off for a common lesion was set empirically at 75 per cent.

In order to process the CT data neuroanatomically, the smallest cumulative lesions were then depicted on a schematic drawing of the human brain. The horizontal cuts were transferred onto a sagittal mask with orbitomeatal line coordinates obtained from 25 brains (Keyserlingk and Lange, 1979). The most frontal and the most sagittal points of the cumulative lesion and the insular cistern in each standardized CT slice were then projected onto the corresponding levels of the sagittal mask. By connecting these points, the area between the horizontal levels in the sagittal mask was interpolated linearly. The schematic drawings (*see* fig. 1) thus obtained could give a lateral view of the cumulative lesion and of the insular cistern.

In order to arrive at frontal projections, four frontal cuts corresponding to Matsui and Hirano (1978, pp. 425–419) were marked in the sagittal cuts at 0.5, 1, 1.6 and 2.2 cm in front of the meatal line. With reference to the individual standardized CT slices as well as to the sagittal mask, the distance from the midline was measured for anteroposterior extension of the lesion, the ventricular space and the insular cistern, and mapped onto the corresponding frontal image. The resulting points were again connected and yielded the extent of the lesion and the ventricular space in the frontal view. Finally, additional structures, such as the basal ganglia, again taken from Matsui and Hirano, were added to illustrate the pertinent topographical relationships.

In order to construct a comparable representation of Leborgne's lesion, we relied upon the CT information published by Castaigne *et al.* (1980). Since frontal cuts were given in the publication, it was necessary to project the lesion on schematic horizontal cuts corresponding to our standardized CT scans (fig. 2).

TABLE 2. SAMPLE CHARACTERISTICS OF CV PATIENTS, STANDARD GLOBALS AND BROCA'S APHASICS

Sample population	*Statistic*	*Age (yrs) at AAT*	*Interval (months) Onset/AAT*	*Interval (months) Onset/control CT*
CV patients	Median	67.5	2	16.5
(n = 8)	Range	(51-73)	(1-35)	(1-35)
Standard globals	Median	53.5	3.5	11
(n = 32)	Range	(34–75)	(1-98)	(1-98)
Broca's	Median	57	2	3
(n = 15)	Range	(38-68)	(1-24)	(1-14)

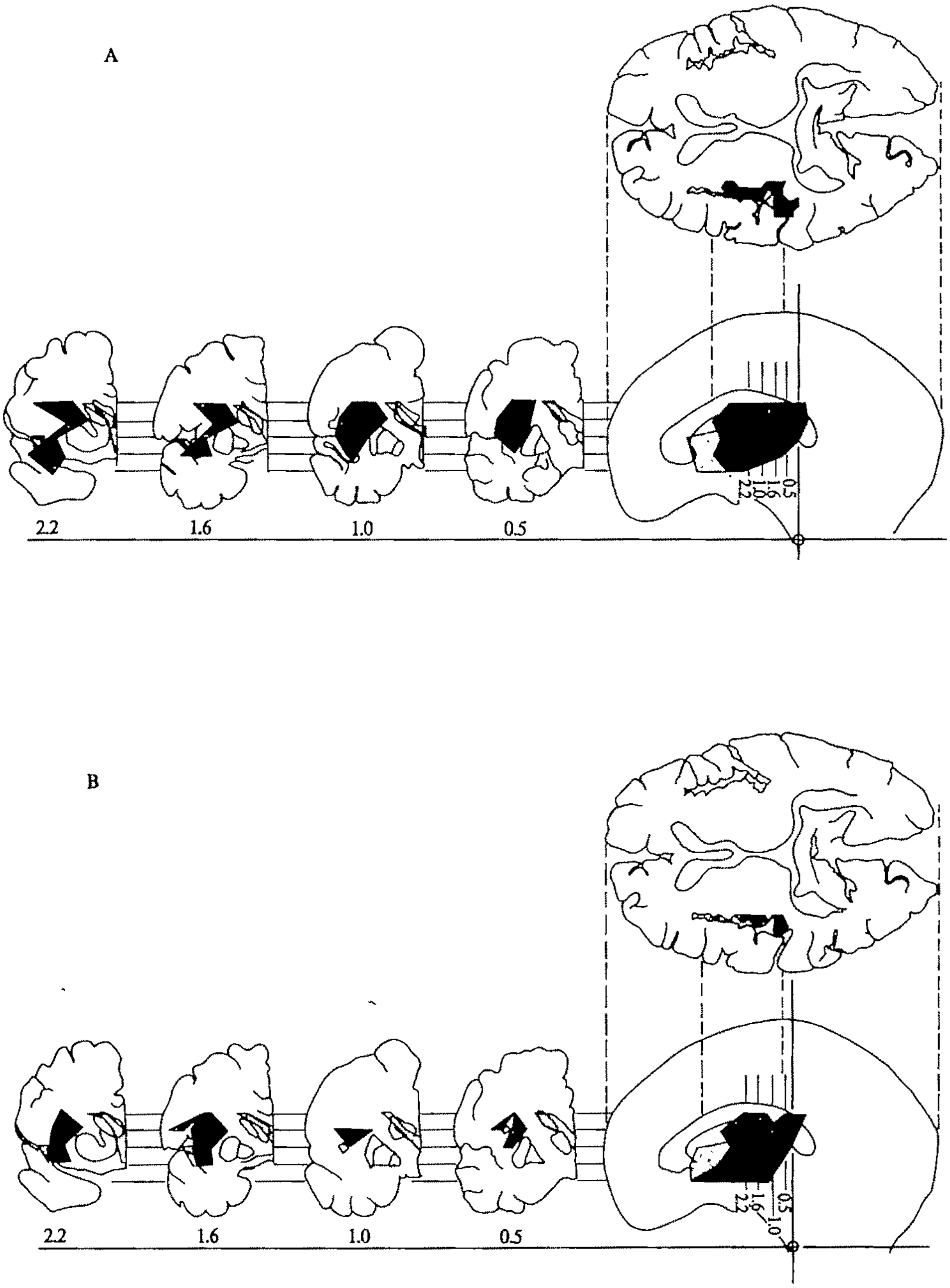


FIG. 1. Sagittal and frontal projections of the smallest cumulative lesions based on standardized horizontal CT scans. The reconstruction is taken from 5 CT slices. For details of the procedure, *see text.* Only slice 3 is shown for illustrative purposes. A, CV speech production. B, standard global aphasia. Darker area = insular cistern. Hatched area = cumulative lesions.

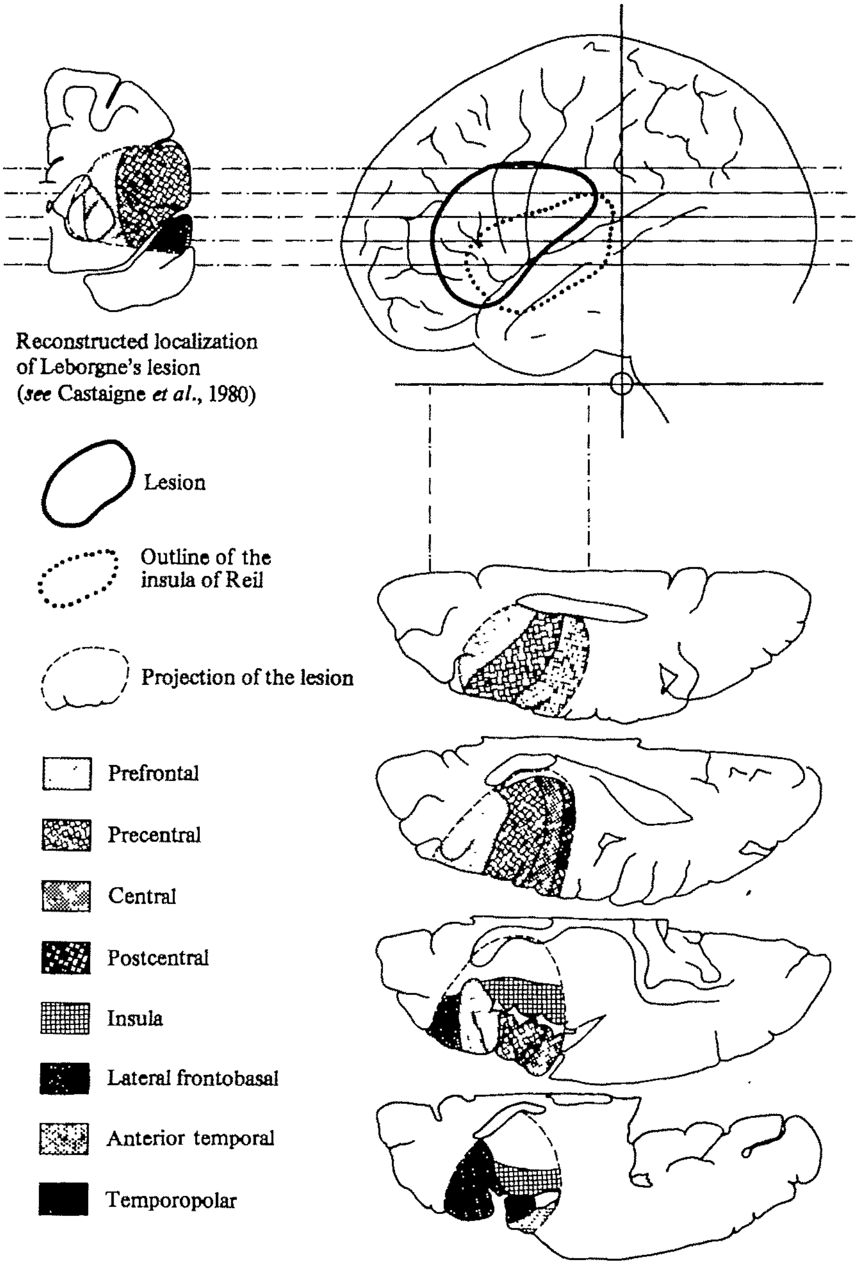


FIG. 2. Sagittal and horizontal reconstruction of Leborgne's lesion based on frontal cuts, as published by Castaigne *et al.* (1980). For illustration only one frontal cut is given.

RESULTS

Neurolinguistic Status of Patients with CV Speech Production

Spontaneous speech production could not be evaluated according to any linguistic criteria, because the only remaining element, namely one and the same CV syllable, is so primitive that no phonological, semantic or syntactic features can be identified. Consequently, scores were zero for each rating level of the subtest spontaneous speech, with the exception of articulation and prosody, where rating was possible and varied from 2 to 5, the latter score indicating no disturbance. Low scores were given in cases of severe dysarthria (*see* Table 3, Cases 3, 4, 5 and 8). For half of the patients, a variety of intonation patterns could be perceived by ear in the fluently repeated syllables. These patterns varied across patients and also in the production of each individual patient. A detailed analysis of the prosodic qualities of CV recurring utterances is in progress. In dialogue situations, 7 out of 8 patients were able to maintain turntaking conventions, that is, they did not interrupt the partner but instead produced their utterance when it was their turn.

On the other subtests of the AAT there was somewhat more variability among patients as well as across subtests. The percentile ranks in Table 3, however, show that all patients were severely disturbed in every modality. In particular, there was also a severe comprehension deficit, a finding which is at variance with Broca's (1861*a*) famous dictum, that Leborgne 'understood everything said to him'.

Aphasiological Status of Patients with CV Speech Production

AAT performance of our CV patients was compared with the performance of patients with standard global aphasia and with Broca's aphasia (Table 4). Verbal communicative ability was zero for most of the patients with standard global

TABLE 3. AAT RESULTS OF PATIENTS WITH CV RECURRING UTTERANCES

	*Spontaneous speech ratings (0–5)**						*Percentile ranks on AAT subtests***				
Case	*Comm*	*Art/Pros*	*Aut*	*Sem*	*Phon*	*Syn*	*TT*	*Rep*	*Writ*	*Name*	*Comp*
1	0	4	0	0	0	0	14	2	8	9	15
2	0	5	0	0	0	0	12	13	22	9	24
3	0	2	0	0	0	0	20	6	27	9	13
4	0	2	0	0	0	0	29	4	8	9	15
5	0	5	0	0	0	0	6	2	8	9	9
6	0	5	0	0	0	0	12	2	8	9	12
7	0	2	0	0	0	0	19	15	10	22	6
8	0	2	0	0	0	0	12	2	8	8	1

* Rating scales are abbreviated as follows. Comm = verbal communication; Art/Pros = articulation and prosody (both aspects are rated on one scale because dysarthria usually causes dysprosody). Aut = automatic speech elements. Sem = semantics. Phon = phonology. Syn = syntax. ** AAT subtests are abbreviated as follows. TT = token test. Rep = repetition. Writ = written language (reading and writing). Name = confrontation naming. Comp = auditory and reading comprehension.

aphasia and for all CV patients, while it was considerably better for Broca's aphasics. The same was true for the ratings on the different linguistic levels of semantics, phonology and syntax. Broca's aphasics also took less recourse to automatic speech elements than CV patients and standard global aphasics. The findings were similar for the subtests of the AAT, where again CV patients and standard global aphasics obtained only very low scores, in contrast to Broca's aphasics. In particular, language comprehension was well above average for Broca's aphasics.

On the basis of these test results, we conclude that CV patients have to be classified as a variant of global aphasia. They can certainly be clearly distinguished from Broca's aphasia. The *a posteriori* classification of the patients with the ALLOC program confirmed this clinical classification at 100 per cent. In this respect, our findings are at variance with Alajouanine (1956) and Code (1982).

TABLE 4. AAT RESULTS OF CV PATIENTS, STANDARD GLOBALS AND BROCA'S APHASICS

		ALLOC classification		*Spontaneous speech ratings (0–5)**						*Percentile ranks on AAT subtests***				
Sample population	*Statistic*	*Global*	*Broca*	*Comm*	*Art/Pros*	*Aut*	*Sem*	*Phon*	*Syn*	*TT*	*Rep*	*Writ*	*Name*	*Comp*
CV patients	Median	100	0	0	3	0	0	0	0	13	3	8	9	15
(n = 8)	Range	(100)	(0)	(0)	(2–5)	(0)	(0)	(0)	(0)	(6–29)	(2–15)	(8–27)	(8–22)	(1–24)
Standard globals	Median	100	0	0	2	1	1	1	0	13	9	8	10.5	15
(n = 32)	Range	(79–100)	(0)	(0–2)	(0–5)	(0–4)	(0–3)	(0–4)	(0–2)	(0–37)	(2–27)	(8–44)	(9–41)	(1–41)
Broca's	Median	0	97	3	2	4	3	2	2	52	46	45	58	65
(n = 15)	Range	(0–17)	(74–100)	(1–3)	(2–3)	(0–5)	(1–4)	(2–5)	(1–4)	(53–95)	(13–72)	(20–78)	(18–83)	(30–91)

* Rating scale abbreviations, *see* Table 3. ** AAT subtest abbreviations, *see* Table 3.

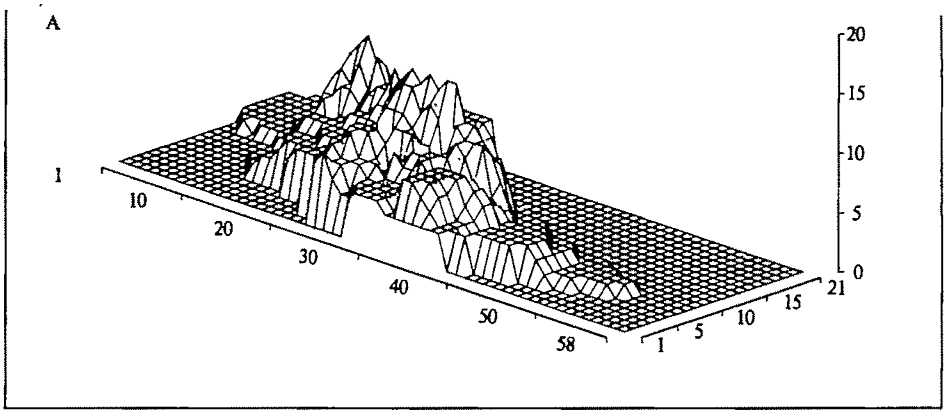
Localization of Brain Lesions

By means of the CT standardization method (Blunk *et al.*, 1981) graphic representations of the cumulative lesions were produced for all three patient groups (fig. 3A, B, C).

There was no striking difference in localization of lesion between standard global aphasics and CV patients, while the lesion in Broca's aphasia clearly differed from both types of global aphasia by its marked frontal and subcortical extension.

A typical lesion could be recognized only for Broca's aphasia. The lesions in CV and standard global aphasia differed from that of Broca's aphasia but not from each other. So far, these localization data are in agreement with the aphasiological findings, namely that CV patients are similar to standard global aphasics and differ from Broca's aphasics.

Also, no significant difference was found between the lesion of standard global aphasia and CV patients when the following relative criterion was used: an anatomical area was considered to be affected when at least 30 per cent of the coordinate points had an entry of 1. Using this reduced information, the lesioned areas showing a high frequency were restricted to the perisylvian region. This finding is comparable to the points of highest frequency depicted in fig. 3, where unreduced information was used. Both figs. 3 and 4 show that only few areas were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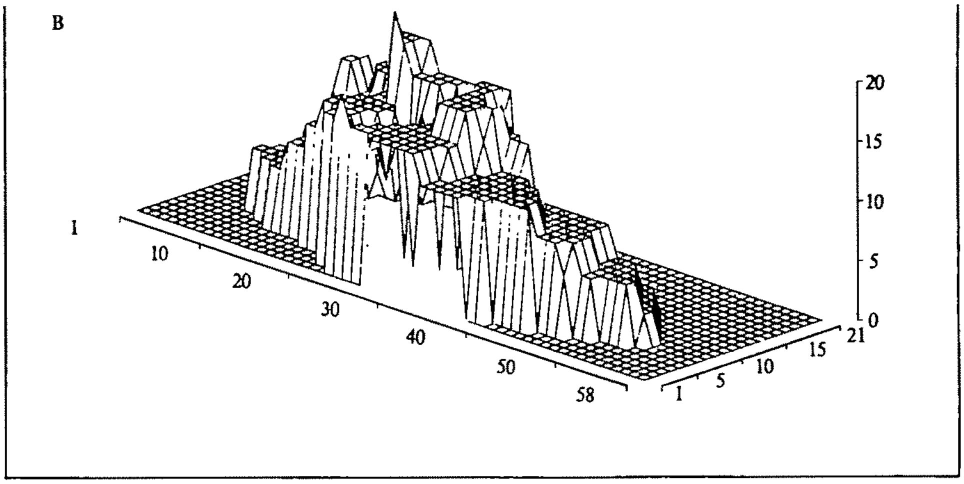
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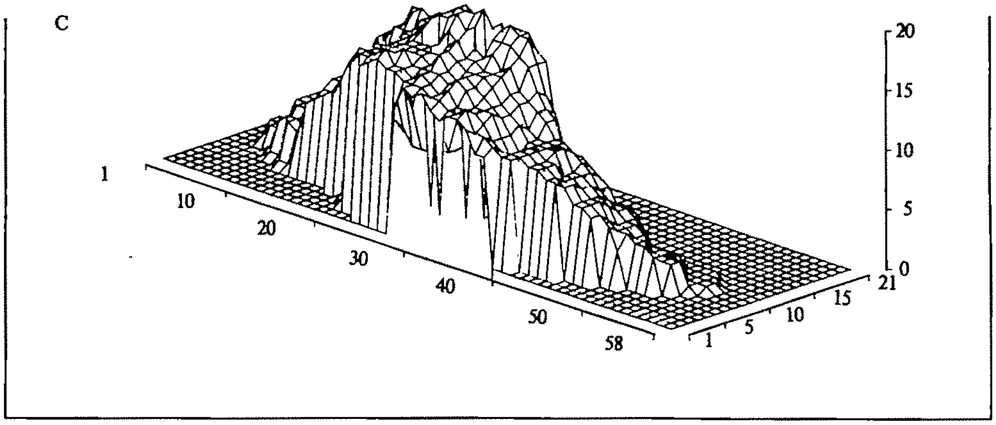
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TABLE 5

Area Information Stored per Slice

Abbr.	*Anatomical area*	*Slice* 1	2	3	4	5
Fs	Superior frontal gyrus	+	+	+	+	+
Fm	Medial frontal gyrus	+	+	+	+	+
Fi	Inferior frontal gyrus	+	+	+	+	+
Mf	Frontal white matter	+	+	+	+	+
Cr	Central region				+	+
Sm	Supramarginal gyrus				+	+
Nc	Caudate nucleus				+	+
Pp	Putamen and pallidum		+	+		
Th	Thalamus		+	+		
Of	Frontal operculum			+		
I	Insula		+	+		
We	Wernicke's area			+		
Sy	Sylvian fissure	+	+			
A	Angular gyrus					+
Ts	Superior temporal gyrus	+	+	+	+	+
Tm	Medial temporal gyrus	+	+	+	+	+
Ti	Inferior temporal gyrus	+	+	+	+	
Oc	Occipital gyrus	+	+	+	+	+
Mp	Posterior white matter	+	+	+	+	+

Artery Information Stored per Slice
Branches of the Middle Cerebral Artery*

Abbr.	*Cortical branch*	*Slice* 2	3	4	5
Fl	R. frontobasalis lateralis	+	+		
Pf	R. prefrontralis		+	+	+
Sp	R. sulci precentralis (prae-Rolandii)		+	+	+
Sc	R. sulci centralis (Rolandii)		+	+	+
So	R. sulci postcentralis (post-Rolandii)			+	+
Pa	R. parietalis anterior			+	+
Pp	R. parietalis posterior, R. gyri angularis			+	+
To	R. temporooccipitalis	+	+	+	+
Tp	R. temporalis posterior	+	+		
Ti	R. temporalis intermedius	+			
In	R. insulares	+	+		
Ta	R. temporalis anterior	+			
Tl	R. temporopolaris	+			

* The vascularization regions were defined by Professor Dr Graf von Keyserlingk, Department of Anatomy, RWTH Aachen based on Szikla *et al.*, 1977.

FIG. 3 (*opposite*). Graphic representation of absolute frequency of lesion points per syndrome in standardized CT slice 3. A, Broca's aphasia. B, global aphasia with CV speech production. C, standard global aphasia. Lateral view of left hemisphere. 1–58 = longitudinal axis; 1–21 = transverse axis; 0–20 = number of patients. Landmarks on longitudinal axis: 7–14 = inferior frontal gyrus; 16–22 = frontal operculum; 22–32 = superior temporal gyrus; 32–45 = middle temporal gyrus; 45–52 = inferior temporal gyrus; 52–58 = occipital cortex. Note identical extension of lesion in both groups of global aphasia. The plateaux in the representation of CV patients' lesions are an artefact of the smaller number of patients. In contrast, the frequency of lesion points in patients with Broca's aphasia has a more frontal and almost exclusively subcortical peak. For ease of comparison all three subgroups have been adjusted to the same scale.

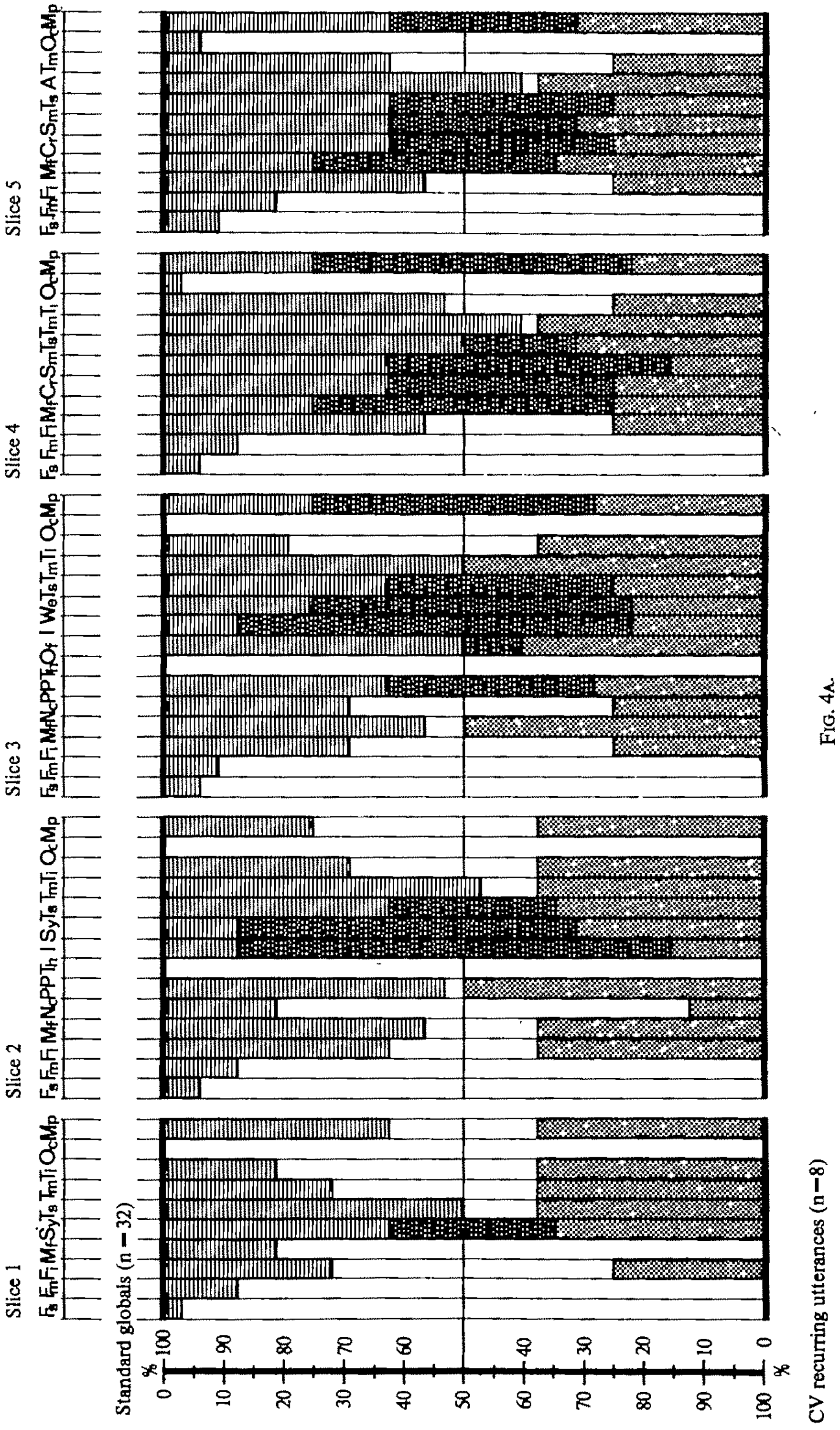

Slice 1
Fs Fm Fi Mf Sy Ts Tm Ti Oc Mp
Slice 2
Fs Fm Fi Mf Nc P PT Th I Sy Ts Tm Ti Oc Mp
Slice 3
Fs Fm Fi Mf Nc P PT Th Of I We Ts Tm Ti Oc Mp
Slice 4
Fs Fm Fi Mf Cr Sm Ts Ts Tm Ti Oc Mp
Slice 5
Fs-Fm Fi Mf Cr Sm Ts Ts A Tm Oc Mp
Standard globals (n = 32)
%
0
10
20
30
40
50
60
70
80
90
100
100
90
80
70
60
40
30
20
10
0
%
CV recurring utterances (n = 8)

FIG. 4A.

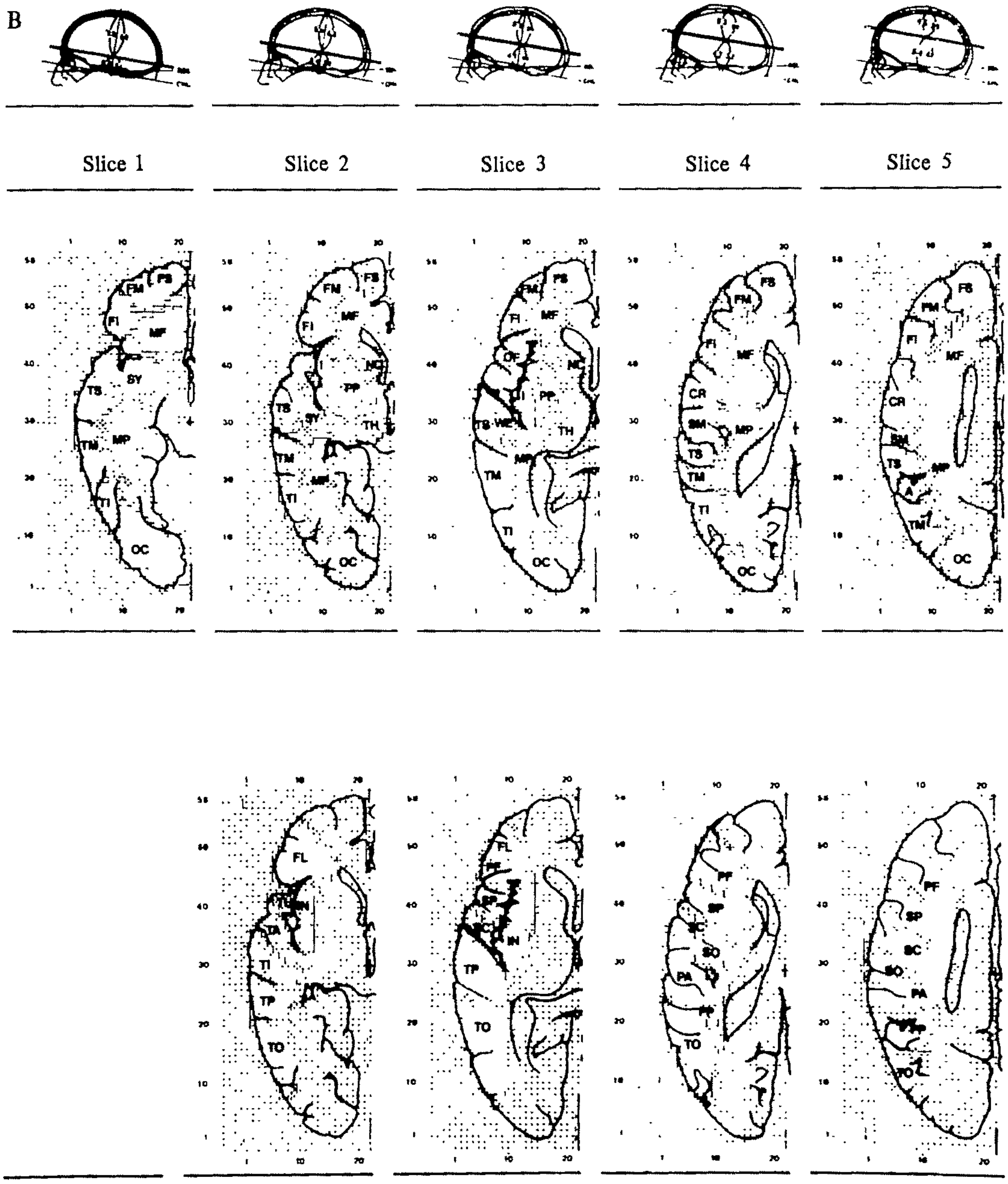


FIG. 4. A, lesioned areas per syndrome using the 30 per cent criterion (*see text*) for patients with standard global aphasia and with CV production. An area was considered to be affected if at least 30 per cent of its coordinate points had 1/0 entries. B, *upper*, 5 standardized CT slices with defined anatomical areas. Lower, 4 standardized CT slices with defined vascularization territories from the middle cerebral artery. The abbreviations used for the names of anatomical areas in A and B (*upper*) and for the vascularization territories in B (*lower*), together with the information stored per slice, are given in Table 5.

lesioned in more than 75 per cent of the patients, namely the insular region, the bank of the sylvian fissure and the frontal white matter, Wernicke's area, the adjacent superior temporal cortex and the temporoparietal white matter.

On the basis of figs. 1 and 2 a comparison was made of the cumulative lesions in CV patients and standard global aphasics as well as of Leborgne's lesion. In the literature it has repeatedly been maintained that there is a relation between a lesion of the basal ganglia and repetitive behaviour (Kornhuber *et al.*, 1979; Brunner *et al.*, 1982; Kirkby, 1969). We therefore examined the frontal representations with a view to detecting any possible differential affection of the basal ganglia in CV patients and standard global aphasics. The findings were negative in this respect.

Another important problem is the role of insular lesions for different subtypes of aphasia (Goldstein, 1915; Mazzocchi and Vignolo, 1979; Kertesz *et al.*, 1979; Damasio and Damasio, 1980; Naeser *et al.*, 1982). The insular cortex was one of the major overlapping areas in standard global aphasia, in global aphasia with CV as well as in Broca's aphasia. It remains an open question as to whether this finding indicates a crucial role of the insula for language function or whether the lesion of the insula is merely an epiphenomenon related to the vascular distribution of the middle cerebral artery. Leborgne's lesion fits well into the picture of both subgroups of global aphasics.

The traditional view that the lesion underlying global aphasia is a large one, extending from Broca's to Wernicke's area, is only true for the cumulative representation. However, when the individual lesions are compared with the cumulative ones, there is great variability in size and localization. Both in standard global aphasia and global aphasia with CV, the individual lesions are large and small, anterior and posterior, single and multiple. Examples are given in fig. 5.

In some cases the lesion is not different from the one typically underlying Broca's aphasia, that is, the insular region and subcortical white matter of the lateral frontal lobe (a, b). There are also some global aphasics with a still smaller lesion restricted to the lentiform nucleus (h), others with a lesion typical for Wernicke's (c, d) and even for transcortical sensory aphasia (e).

The individual drawings demonstrate that the procedure of superimposing lesions in these subgroups of aphasia, in contrast to Broca's and Wernicke's aphasia (Blunk *et al.*, 1981; Mazzocchi and Vignolo, 1979; Kertesz *et al.*, 1979), does not enhance the typical lesion but rather leads to a loss of significant information.

DISCUSSION

The neurolinguistic and aphasiological status of patients who produce exclusively CV syllables has not yet been defined empirically in the literature. When describing 'disorders of phonemic production', Hécaen and Albert (1978) mentioned patients who produce 'only a limited range of meaningless phonemes or syllables', and in this connection they refer to Broca's patient 'Tan-Tan'.

Our findings allow us to make more precise statements. In the patients described here, there is not even a limited range of minimal linguistic units. There is only one recurring syllable, consisting of one and the same consonant and vowel which do not even have the status of phonemes. Phonemes are the minimal linguistic elements that distinguish meaning, like /c/at *vs* /r/at. It is only within a system of phonemes that a language sound can serve this function. This is not the case in recurring CV speech production.

Further research into the neurolinguistic status of CV utterances should take into account to what extent the consonants and vowels used depend on the phonological system of the specific languages. Broca's case 'Tan-Tan' with his nasal vowel seems to be indicative of a certain language specificity, whereas our sample did not include nasal vowels, which do not belong to the phonological repertoire of the German language. Furthermore, the emphasis on the expressive aspect of language implied by the heading 'disorders of phonemic *production*' (Hécaen and Albert, 1978) suggests that these patients should be classified as Broca's aphasia, which these authors actually do (p. 36). Performance on the AAT, however, clearly shows that these patients do not have Broca's aphasia but rather global aphasia with no elements of the language system (phonemes, morphemes, syntactic structure) left intact. Even the primitive automatic speech elements mentioned by Jackson are absent. An extremely severe disturbance is not only found in language production, but also in comprehension.

Does Leborgne fit into this picture, considering that he was reported to 'understand almost everything said to him'? We have never seen a patient with recurring utterances and good language comprehension. This seeming contradiction can, in our view, readily be explained by the limited demands on comprehension made on a patient institutionalized for twenty-one years in an asylum of the mid-19th century.

Sometimes, and very rarely so, a patient with Broca's aphasia and very severe oral apraxia produces a very limited set of phonological neologisms which have a superficial similarity to CV recurring utterances. Closer analysis, however, clearly shows a certain variety of vowel and consonant repertoire, so that these patients are quite different from Broca's original observation.

Although patients with CV production and standard global aphasics have a quite similar testing profile in the AAT, there are striking differences in several aspects of their oral expression. Overall fluency of output and, to a lesser extent, intonation contours, are well preserved in CV patients in contrast to the laborious, monotonous, nonfluent speech production of standard global aphasics. This enables the patients with CV to participate in those aspects of communicative interaction which rely on prosodic features and fluency, even though their language systematic repertoire is reduced to the most elementary language remnant, one CV utterance, which just functions as a fluency and thereby as a prosody carrier. Compared with standard global aphasics, patients with CV utterances are much more impaired in one respect and less so in another. If we propose that there are two varieties of global

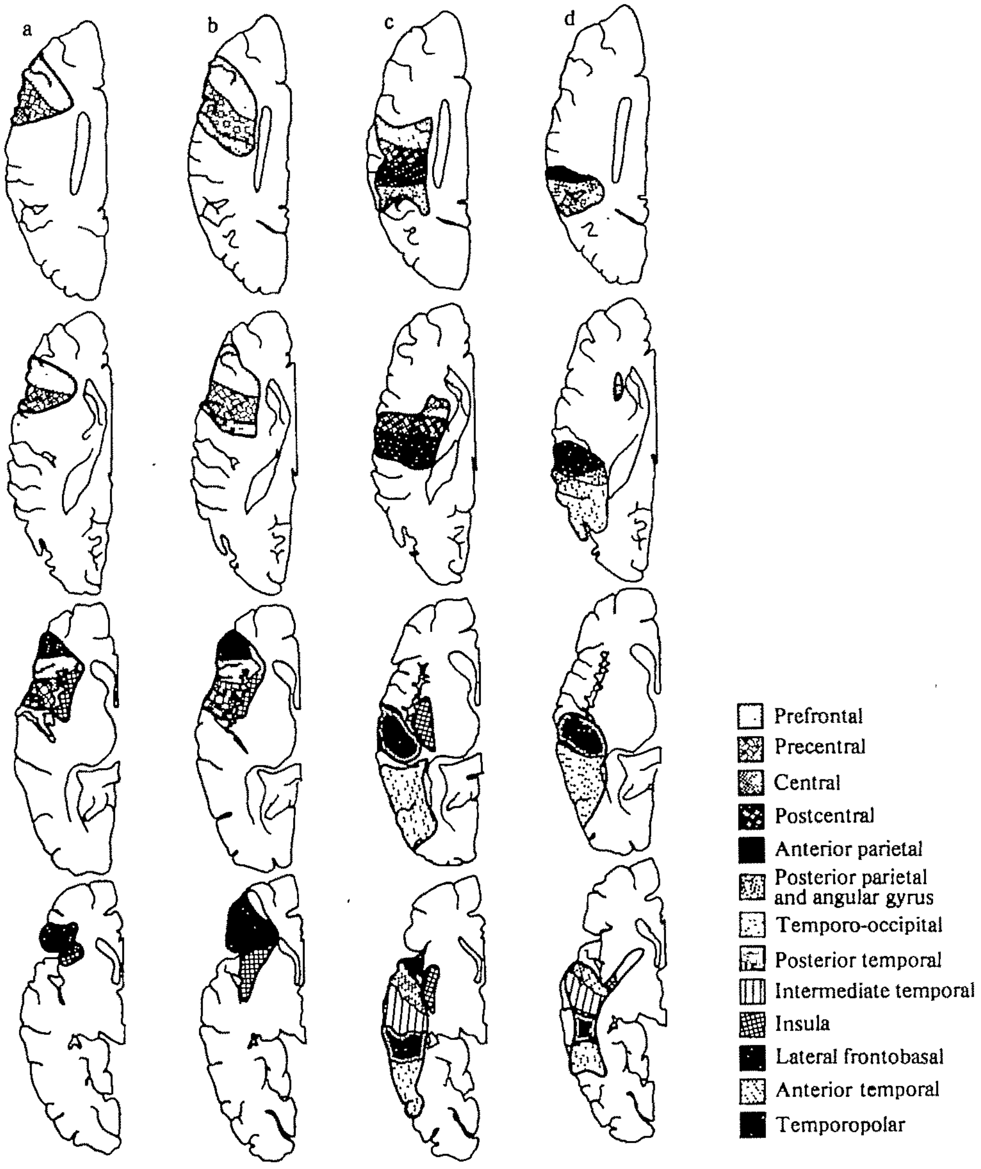
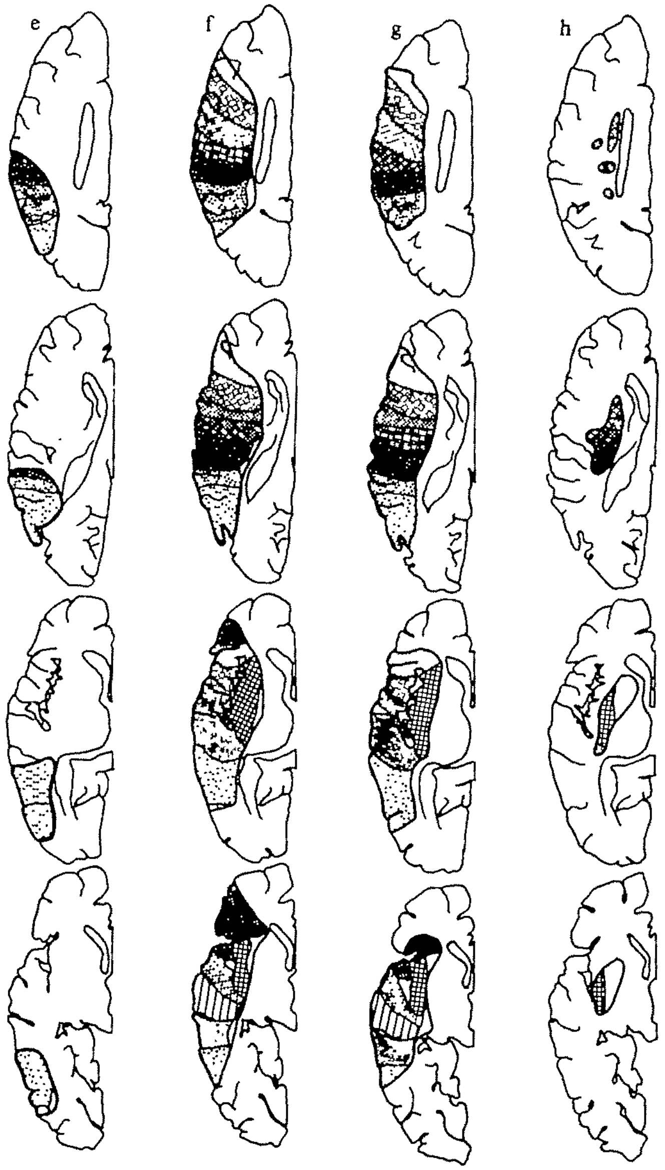


FIG. 5. Variability of lesion in patients with CV production and standard global aphasia. Illustrative examples showing lesions similar to those in Broca's aphasia (a, b), Wernicke's aphasia (c, d), transcortical sensory aphasia (e), 'typical' infarction of middle cerebral artery (f, g) and isolated basal ganglia lesion (h).


e
f
g
h

aphasia, standard nonfluent and nonstandard fluent, where do we then classify Jackson's (1879–1880) patients and Broca's second patient Lelong (1861*b*), who had a similar repertoire? The decision depends on the fluency and prosodic quality of their output which unfortunately was not reported. In our experience, recurring utterances which are produced exclusively and not only occasionally, be they CV syllables or somewhat richer utterances, are always concatenated and consequently fluent.

The difference between nonfluent and fluent global aphasia also shows in spontaneous recovery and the results of speech therapy. Whereas it is not unusual for standard global aphasics to recover to a state where they reacquire some communicative ability and language comprehension, this evolution is never observed in patients with CV production. Even when they receive intensive speech therapy, improvement is extremely slow and limited. They are able to learn some short phrases, such as 'a cup of coffee', but they will use them in inadequate situations and will always relapse into their recurring utterances. In the subtests of the AAT there is virtually no improvement. We have never seen the stages of recovery described by Alajouanine (1956) nor a change in the recurring utterance as described by this author (Table 6).

The designation of these patients as nonstandard fluent raises the question how they can be fluent in a setting otherwise characteristic of global aphasia. A possible explanation would be that this small subgroup of aphasics, which amounts to about 1 per cent of our aphasic population, has premorbidly an atypical organization of language in the brain. It could be speculated that in these patients there is a differential degree of specialization for different expressive language functions. The language systematic functions would be strictly lateralized in the left hemisphere,

TABLE 6. RECOVERY DATA ON PATIENTS WITH CV RECURRING UTTERANCES

Case	*Interval (months) Onset/AAT*	*Speech Therapy (months)*	*Percentile ranks on AAT subtests**				
			TT	*Rep*	*Writ*	*Name*	*Comp*
1	1	0	14	2	8	8	15
	12	8	14	2	8	9	17
	24	20	14	2	8	9	7
3	1	0	20	6	27	9	13
	17	0	33	2	23	10	35
5	1	0	6	2	8	9	9
	5	2	12	22	8	9	18
	17	14	8	37	13	16	8
6	1	0	12	2	8	9	12
	20	0	23	7	8	9	14
	29	2	20	12	8	9	15
	41	14	17	20	12	10	7

* AAT subtest abbreviations (*see* Table 3).

whereas fluency, like prosody, is organized either bilaterally or in the right hemisphere. Following the left-sided brain lesion, some area in the right hemisphere would just continue to mediate the patient's speech intent with the fluency and prosody features available. This speculation would be supported by the observation that the striking fluency of patients with recurring utterances is there from the beginning and does not develop as a compensatory mechanism.

The speculation that patients with CV production do have an abnormal brain organization cannot be substantiated at present, because this subgroup of aphasia is very small. Furthermore, as is the case with all global aphasics, the patients are extremely difficult to test for other cognitive functions.

Leaving aside the problem of abnormal interhemispheric specialization, further speculation could be made on intrahemispheric mechanisms that produce fluency and prosody in these patients. Fluency is a characteristic feature of Wernicke's aphasia. There is a subgroup of Wernicke's aphasia, almost as rare as patients with CV production, who produce phonemic jargon. Could our patients have phonemic jargon reduced to one CV syllable? This consideration would suggest that they are a subgroup of Wernicke's and not of global aphasia. However, Wernicke patients with phonemic jargon do not produce jargon exclusively, but only predominantly. They also produce real words, fragmentary sentences and stock phrases, indicating that they have some morphology, some phonotactic rules and some elementary syntax available. Furthermore, the patients with phonemic jargon show a recovery pattern toward semantic jargon and finally to standard Wernicke's aphasia which is never the case with CV patients.

The inadequacy of the explanations offered so far leads to a reexamination of the nature of prosody and fluency in patients with CV speech production. Closer observation of the prosodic quality shows that there is some variability in intonation patterns in most patients (Poeck and de Bleser, 1983). It is highly questionable, however, that prosodic features are used by these patients for communicating speech intentions such as questions, statements or requests. It rather seems to be the case that the nonaphasic partner tends to overinterpret the communicative value of these intonation contours.

A similar consideration holds true for fluency. Fluency by itself has no communicative function. It only facilitates communication provided there are diversified language elements available. This is not the case when one and the same CV syllable is produced in a perseveratory manner.

The examination of the underlying brain lesion by means of the graphic representation of the CT lesion did not permit a differentiation between standard nonfluent and nonstandard fluent global aphasia. This holds true for the cumulative as well as the individual representations. Definitely, neither size nor location of the CT lesion determines whether a patient will have one or the other variety of global aphasia. At least that is the conclusion at the present state of our investigation based on different kinds of processing of CT information.

Leborgne's lesion is compatible with the lesion of some patients in either group.

On the other hand, the lesion in many of our patients is quite different from Leborgne's. Therefore, Leborgne's lesion represents just one of the many variations we have found in both subgroups of global aphasia.

These findings show that the widely used technique of superimposing lesions in order to find one common denominator is not the adequate approach when one and the same syndrome arises from lesions at distant sites of the left hemisphere. This is the case with global aphasia in its two varieties. Here, the localizational problem is not which is *the* typical lesion but rather which structures are affected by the different lesions found in patients with identical aphasic features. Obviously, this statement implies that in global aphasia with small and variable lesions critical cortical areas are disconnected. Since pathways are not visualized in the CT scan, the lesions have to be reconstructed graphically. The most appropriate procedure appears to be three-dimensional reconstruction (Keyserlingk *et al.*, 1983).

If a disconnection cannot be demonstrated, there is an alternative hypothesis, namely, that the anatomically small CT lesions do not reflect the true extent of functional brain damage. This speculation would require PET scan examinations in comparison with CT scans.

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CONDUCTION BLOCK AND DENERVATION IN GUILLAIN-BARRÉ POLYNEUROPATHY

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SUMMARY

The two main electrophysiological abnormalities seen in the first two weeks of the acute Guillain-Barré syndrome (GBS) were conduction block and, in some patients, low maximum M response amplitudes. In this study period, maximum motor and sensory conduction velocities were often in the normal range and temporal dispersion was relatively less common. The conduction block was generalized in its distribution in some peripheral nerves, while in others the block was predominantly proximal or distal in location. Conduction abnormalities in excess of those proximal or distal to it were frequent at common sites of entrapment. Very low M response amplitudes early in the course of the disease correlated well with the subsequent development and frequency of denervation in the muscle(s) and unfavourable clinical recovery. We conclude that conduction block is the main cause of the acute paralysis and sensory loss in the GBS. Axonal degeneration contributes variably to the acute disorder, but is the main cause of lasting disability.

INTRODUCTION

The two main mechanisms which best explain the weakness and loss of sensation in the Guillain-Barré syndrome (GBS) are conduction block and, to a lesser extent, axonal degeneration in the peripheral nerves. Conduction block, the block of transmission of impulses in nerve fibres whose axons are intact, is one of the most important consequences of experimental peripheral demyelination (Denny-Brown and Brenner, 1944; Kaeser and Lambert, 1962; McDonald, 1963; Rasminsky and Sears, 1972; Smith and Hall, 1980) and is a prominent characteristic of experimental allergic neuritis (Cragg and Thomas, 1964). Surprisingly, conduction block has not received the attention it deserves in the clinical electrophysiological assessment of this disease despite the early recognition of its importance (Lambert, 1961; Bannister and Sears, 1962).

Other conduction abnormalities which have received more attention in clinical investigations are slower conduction velocities (Lambert, 1961; Lambert and Mulder, 1964; Isch *et al.*, 1964; Humphrey, 1964; Bergamini *et al.*, 1966; McQuillen, 1971; Eisen and Humphreys, 1974; McLeod *et al.*, 1976; Martinez-Figueroa *et al.*,

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1977; McLeod, 1981), increased degrees of temporal dispersion and prolonged F response latencies in limb nerves (Kimura and Butzer, 1975; King and Ashby, 1976). None of these explains the weakness in the initial phase (0 to 4 weeks) of the disease, a period in which conduction velocities are often normal and abnormal temporal dispersion may not be apparent.

Denervation has been reported in the GBS, but the extent and distribution of this has not, with occasional exceptions, been systematically studied (Eisen and Humphreys, 1974; McLeod *et al.*, 1976). The question of axonal degeneration is important because post-mortem examinations reveal clear evidence in some cases of wallerian degeneration in peripheral nerve fibres and reactive changes in and sometimes loss of anterior horn cells (Haymaker and Kernohan, 1949; Asbury *et al.*, 1969). These changes, although perhaps less severe in survivors, are in all likelihood important sources of residual motor disabilities in this disease.

The main objectives in this investigation were to learn about the incidence, localization and degree of conduction block and denervation in GBS and to correlate these electrophysiological abnormalities where possible with the clinical outcome. Our investigations clearly demonstrated the presence of conduction block and often denervation in these patients in whom conventional measurements of conduction velocities were normal.

One other objective was to measure conduction in the peroneal, ulnar and median nerves at the levels of their common entrapment sites to look for conduction abnormalities in excess of those proximal and distal to these locations. Disproportionate local conduction abnormalities could indicate local injury to the nerves at these levels. This is important because local compression injuries could themselves produce wallerian degeneration in the nerves together with denervation and lower amplitude maximum M responses in the affected muscles.

Some aspects of this study have already appeared in abstract form (Brown *et al.*, 1981*a*, *b*).

METHODS

Subjects

Twenty-five patients, each of whom met the NINCDS criteria for the diagnosis of the GBS (Asbury *et al.*, 1978), were included.

Electrophysiological Procedures

Measurement of maximum motor conduction velocity. Maximum motor conduction velocity and motor terminal latency were measured in the median, ulnar and peroneal nerves. Stimulation was by means of brief (0.05 to 0.1) percutaneous pulses delivered to the motor nerves at various sites proximal to the innervation zone.

For the ulnar nerve, the levels of stimulation included Erb's point, the proximal upper arm, 20 to 30 mm proximal to the medial epicondyle of the humerus, 10 to 20 mm distal to the cubital tunnel and the wrist. For the median nerve the sites of stimulation included the wrist, elbow and proximal upper arm but not Erb's point. The peroneal nerve was stimulated at the level of the popliteal fossa, fibular head and ankle. Between each of the successive segments in these nerves maximum motor conduction velocity was determined and a judgement made as to the presence or absence of conduction block.

For the ulnar nerve, measurements of conduction distance across the elbow were made with the elbow in 90 deg flexion. Calipers were used to measure the distances between Erb's point and the upper arm and between the root stimulating electrodes and the sciatic nerve stimulation site in the lumbar root stimulation studies. Otherwise all distances were measured with a surface tape.

Maximum motor conduction velocity in the ulnar, median and peroneal nerves was judged to be abnormal when the segments between the elbow and wrist or fibular head and ankle were below the 2 SD lower limit of control subjects for the same segment. Likewise, terminal motor latency in the three motor nerves in excess of the 2 SD longest limit for controls was considered abnormal and prolonged.

Sensory conduction was also assessed, but because conduction block was much more difficult to assess in sensory fibres the results of these studies have been excluded from this study.

Needle electromyography. This was performed in the deltoid, biceps brachii, extensor digitorum communis, thenar, hypothenar, lumbar paraspinal, quadriceps, tibialis anterior, peroneus longus, extensor digitorum brevis (EDB), abductor hallucis and gastrocnemius muscles.

The main objective of the electromyographic examination was to detect and, where present, to quantitate the occurrence of fibrillation potentials. This was based on the assessment of the numbers of fibrillation potentials present at 5 separate sites within each muscle and recorded semiquantitatively as follows: ± = rare, + = occasional, + + = moderate numbers, + + + = frequent fibrillation potentials.

Evaluation of conduction block. The presence of conduction block was based on the demonstration of larger declines in the motor unit response amplitude (and area) than were ever present in control motor nerves over the equivalent segments (*see* Results).

The distribution of the block was considered to be *generalized* where there was clear evidence that the block was present throughout proximal, intermediate and more distal segments of the nerve.

Conduction over the more proximal segments of the peripheral nerve was difficult to test. In ulnar motor axons, conduction block between Erb's point and the proximal upper arm could be assessed because, although median nerve fibres are also stimulated at Erb's point, there is very little pickup at the hypothenar electrode sites by volume conduction of electrical activity from median-innervated muscles. The same is not true, however, for the median nerve, where volume-conducted pickup of ulnar-innervated thenar muscle activity by the thenar recording electrode is substantial.

In the lower limbs, motor conduction was assessed proximal to the popliteal fossa in 2 patients by stimulation at the level of the L2–3 and L4–5 roots and sciatic notch by needle electrodes. To stimulate the sciatic nerve, Disa 13L63 near nerve needle electrodes were used while insulated lumbar puncture (22 gauge) needles inserted into the subarachnoid space at the lumbar levels served to stimulate the ventral roots as well as for collecting CSF for cellular and chemical analysis.

In 10 other subjects rendered quadriplegic by a cervical fracture dislocation and who volunteered for these studies, there was less than a 30 per cent decline in the EBD or gastrocnemius maximum M response amplitudes or areas between stimulus sites at the level of the roots and 100 to 150 mm proximal to their respective motor points.

Recording electrodes. To measure the changes in the M responses and maximum motor conduction velocity, Copeland-Davies surface clip electrodes were chosen. The position of the stigmatic electrode was adjusted near the innervation zone, so that the initial phases of single motor unit potentials and the maximum M responses were negative, and the peak-to-peak amplitude of the M response was maximum. Between successive examinations in control subjects, the amplitudes of the maximum M responses are within 10 per cent of each other and the shape of the potentials is very similar when care is taken to ensure that the recording sites are similar and steps are taken to minimize movement of the underlying muscles.

Clinical Evaluation.

Of the 22 patients included in this investigation, 18 were re-examined clinically over one year after the onset of the illness. Two patients re-examined less than one year later were also included because their clinical outcome seemed clear. One, seen at 52 days, had recovered almost completely, while the other, seen at 140 days, had severe wasting of many muscles and remained bedridden. Muscle strength and bulk were assessed in the thenar, hypothenar and EDB muscles. It is not possible to judge the strength of EDB and the extensor hallucis brevis (EHB) muscles independently of the actions of the extensor digitorum longus and extensor hallucis longus muscles. At follow-up these index muscle groups were judged to be abnormal if there was any obvious wasting or weakness, or both, in these groups.

The overall clinical status of the patients, based on their neurological examinations, were graded as follows.

0 No neurological symptoms or abnormal signs or functional disability.
1 No neurological symptoms or functional disability, but minor abnormalities on neurological examination such as impaired vibration sense or absent tendon reflexes.
2 Minor motor disabilities apparent in the activities of daily living and more obvious neurological abnormalities such as muscle wasting, weakness or proprioceptive sensory loss.
3 Substantial limitations in daily activities as a result of weakness, such as the inability to walk without mechanical aids or being confined to a wheelchair and very obvious residual wasting and weakness.

To compare the clinical status at follow-up with the physiological studies, the patients were scored according to the lowest maximum M potential of any of the index muscles examined including the thenar, hypothenar and EDB muscles (I = > 50% control mean, II = 10–50%, III = < 10%). The presence of wasting in the index muscles at follow-up was also compared with these M potential scores.

RESULTS

Normal Changes in the Maximum M Response Shape and Size

In the ulnar nerves of control subjects (aged 20 to 60 years, n = 30), there was never more than a 20 per cent decline in the maximum M hypothenar potential peak-to-peak (p-p) amplitude, or a 10 per cent decline in the negative peak area (−p), between the most proximal stimulation site at Erb's point and the most distal stimulation site at the wrist (fig. 1). Likewise, over the same distance there was never more than a 15 per cent increase in the p-p or −p duration of the M potential between the above proximal and distal sites of stimulation. Moreover, the percentage changes in M potential amplitude, area and duration per unit length of nerve were similar over proximal, intermediate and distal segments of the nerve. Over the shorter distances, just below the elbow to wrist, upper arm to just proximal to the elbow and Erb's point to proximal arm, the p-p amplitude of the hypothenar M response to the proximal stimulus was never less than 90 to 95 per cent of the response to the next most distal site of stimulation.

Where there was evidence of anomalous innervation no attempt was made to assess conduction block. Equivalent declines in the maximum EDB and thenar M response amplitudes (and areas) were noted in control peroneal and median nerves between stimulus sites in the popliteal fossa and ankle in respect to the peroneal nerve and proximal arm and wrist with respect to the median nerve.

Criteria for Conduction Block

Conduction block was judged to be present when (1) the decline in the amplitude of the maximum M potential between the most proximal and distal sites of stimulation (popliteal fossa and ankle for the peroneal nerve; proximal arm and wrist for the median nerve; and Erb's point and wrist for the ulnar nerve) exceeded 20 per cent and (2) there were no parallel increases beyond the 15 per cent values seen in control motor nerves in maximum M response p-p or −p durations or changes in the shape of the M response to suggest an increase in the degree of temporal dispersion of these potentials. Where such changes were present no comment could be made about conduction block, because the declines in M response area and amplitude could simply have been a product of an increase in temporal dispersion or phase cancellations between component bi- and sometimes triphasic motor unit potentials in the summation M potential.

Conduction Block

In 13 out of 19 patients tested within fourteen days of the onset of the paralysis there was evidence of generalized conduction block in at least one motor nerve (fig. 2). In 15 of 20 of the motor nerves in which such block was demonstrable the decline in p-p amplitude of the M potential between the most proximal and distal

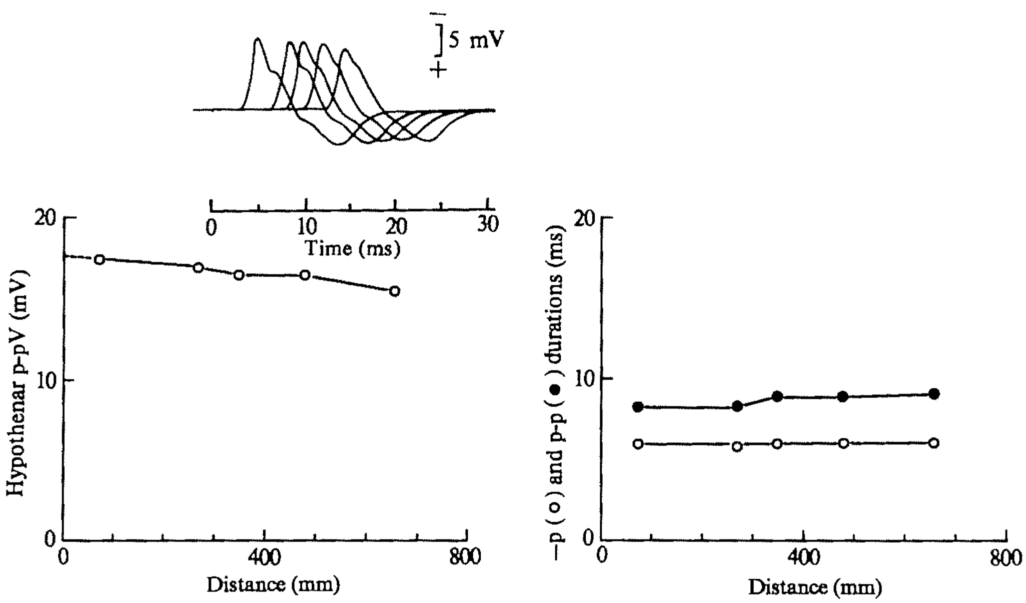

FIG. 1. Normal changes in maximum M potentials, in this case from the hypothenar muscles, evoked by stimulation at sites progressively more proximal to the innervation zone. The recorded potentials are shown in the *inset* and the corresponding changes in the peak-to-peak (p-p) amplitude, negative peak (−p) and p-p duration of the M potentials in response to stimulation at the wrist, below elbow, above elbow, proximal arm and Erb's point sites in the plots.

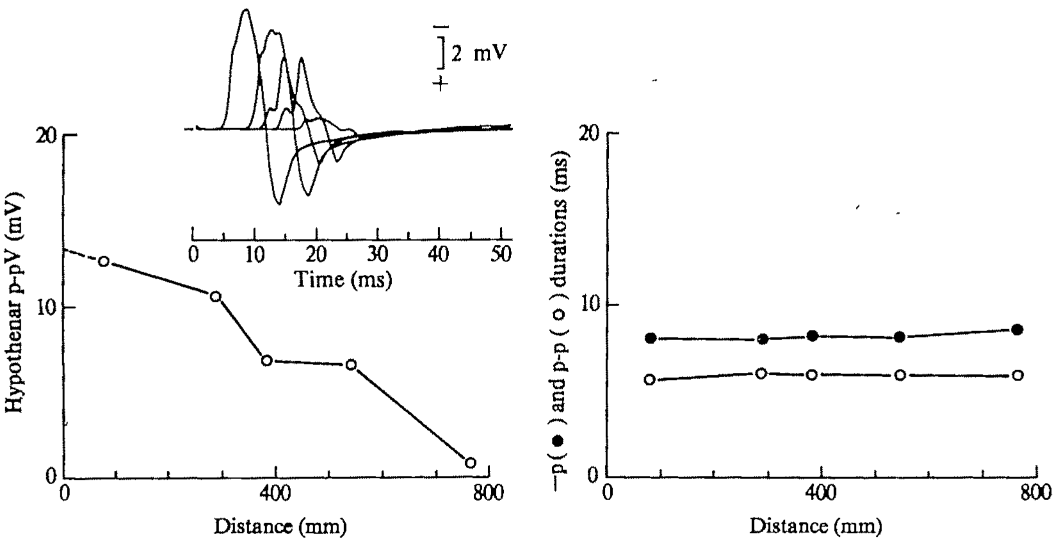

FIG. 2. Patient with Guillain-Barré polyneuropathy examined seven days following the onset of the paralysis. The changes in the maximum hypothenar M potentials elicited by stimulation at progressively more proximal sites, namely the wrist, just distal to the cubital tunnel, just proximal to the elbow, the proximal upper arm, and Erb's point are shown. The recorded potentials are shown in the *inset* and the plots illustrate the changes in the p-p voltage in mV and the p-p and −p durations in ms. Here there was a more than 90 per cent decline in p-pV accompanied by less than a 15 per cent increase in −p or p-p duration between the wrist and Erb's point.

sites of stimulation in the ulnar, median and peroneal nerves exceeded 50 per cent. In none of the above examples did the increases in −p or p-p duration exceed the control upper limits (+15%) established for these nerves.

In one patient in whom M potentials were in the normal range, there was no indication of excessive temporal dispersion or conduction block. In 4 other patients, conduction block could not be assessed properly, either because there were progressive increases in the −p and p-p durations of the M potential evoked at successively more proximal sites of stimulation exceeding normal values (3 patients) (fig. 3) or, as in one patient, there were either no excitable motor axons (median and peroneal nerves) or, in the ulnar nerve, only 2 excitable hypothenar axons remaining at the level of the wrist (fig. 4). The last is an important point because one of the limiting factors in the method of assessing conduction block in this study is that the assessment of conduction in the more proximal portions of the peripheral nerves must necessarily be based on only those motor axons whose impulses are not blocked in the more distal portions of the peripheral nerves. For example, in the extreme instance where only a single motor axon impulse is able to reach the EDB

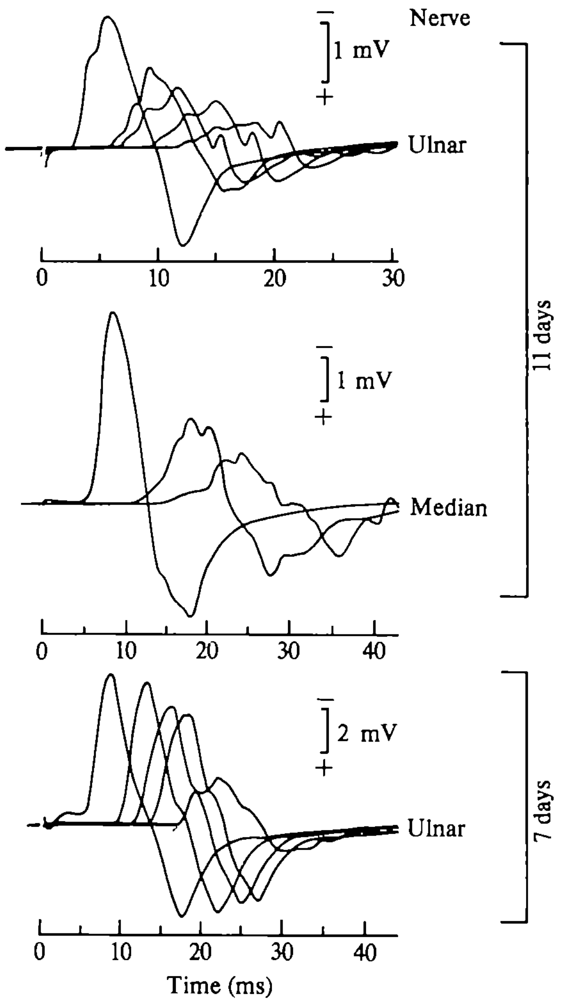

FIG. 3. Examples of excessive temporal dispersion in the maximum M potentials (hypothenar *top* and *bottom* and thenar, *middle*) of subjects with Guillain-Barré polyneuropathy examined within two weeks of the onset of the paralysis. In all 3 examples, the increases in −p and p-p durations exceeded the limits of the changes in control subjects between the wrist and the most proximal stimulation sites, namely Erb's point for the ulnar nerve and the proximal arm for the median nerve.

muscle beyond the fibular head (fig. 5), any assessment of conduction block proximal to the fibular head will depend on the presence or absence of conduction block in this axon!

Proximal Changes in Conduction

In the arm, slowing of motor conduction or conduction block or both in excess (20% or more) of that seen beyond the proximal arm, was present between Erb's point and the proximal arm stimulus sites in 6 out of 16 ulnar nerves in which the assessment was made within two weeks of the onset of paralysis. In one such case the proximal block largely reversed over the next four weeks (fig. 6). In another patient,

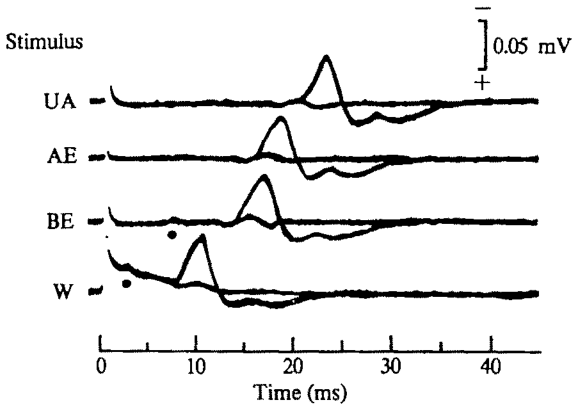

FIG. 4. Guillain-Barré patient examined four days following the onset of paralysis. This patient had only 2 remaining excitable hypothenar motor unit potentials at one week, and throughout subsequent examinations at two, four and twenty-eight weeks. The figure illustrates these two hypothenar motor unit potentials as elicited by stimulation at the wrist (W), below the elbow (BE), above the elbow (AE) and upper arm (UA) levels. In this muscle group and in the thenar and extensor digitorum brevis (EDB) muscles, where there were, respectively 0 and 2 excitable motor unit potentials, abundant fibrillation developed. Despite this, conduction velocities in the 2 remaining hypothenar motor axons were within the 2 SD lower limit of control maximum motor conduction velocity for this nerve, except on the earliest occasion (one week), when maximum velocity across the forearm was 36 m/s. On all 4 subsequent tests over the next fifty days, the terminal motor latencies were prolonged (beyond 3 SD of the upper limits of controls). A prepotential (*see* dot marker), originating in an underlying cutaneous branch of the ulnar nerve, is seen in the BE and W records.

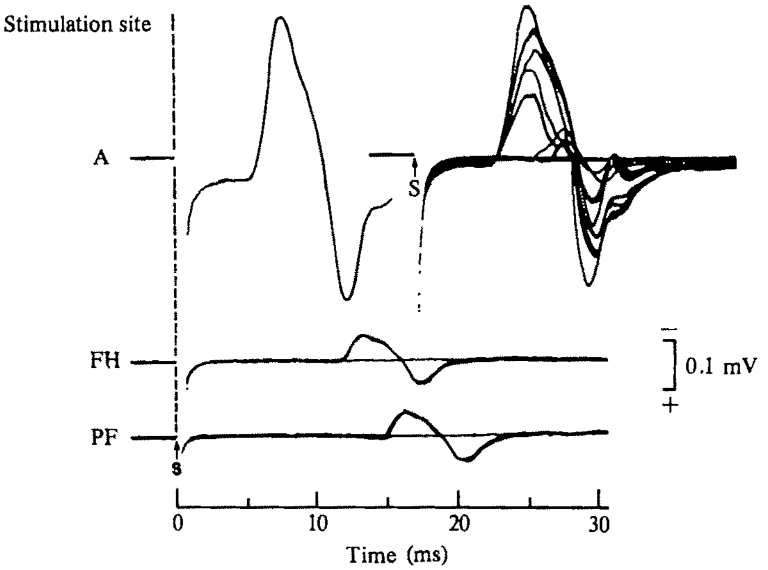

FIG. 5. Guillain-Barré polyneuropathy ten days after the onset of paralysis. The changes in the maximum M potentials in extensor digitorum brevis (EDB) elicited by stimulation at the ankle (A), fibular head (FH) and popliteal fossa (PH) are illustrated. The amplitude of the maximum M potential evoked by stimulation at the ankle was less than 10 per cent of the control mean value for this muscle. Incremental stimulation at the ankle above threshold evoked only 7 successive motor unit potentials, only one of which could be elicited by stimulation at the more proximal levels, indicating conduction block in 6 out of 7 motor axons between the FH and A stimulus sites. Conduction velocity between the popliteal fossa and fibular head was therefore based on conduction in a single motor axon and was 27 m/s, whereas the velocity between the fibular head and ankle was higher at 41 m/s. The lower proximal velocity suggested a possible local injury to the common peroneal nerve between the fibular head and popliteal fossa. It was not clear whether the apparent block in the impulses of 6 of the motor axons proximal to the ankle was the result of demyelination or ongoing axonal degeneration in these fibres, whose excitibility and conductivity had not yet been lost distal to the ankle.

the conduction block between Erb's point and the proximal arm in the ulnar nerve was the only evidence of conduction block in the 3 motor nerves tested.

The segment between the spinal cord and Erb's point could not be assessed by the techniques of this study. In 2 patients seen within two weeks of the onset of the paralysis the lumbosacral roots were stimulated direct, enabling an assessment to be made about conduction in EDB motor axons proximal to the popliteal fossa. In these, the amplitudes of the maximum M potential evoked by stimulation at the levels of the roots or sciatic notch were less than 16 per cent of the maximum M potential evoked at more peripheral stimulus sites. However, these reductions in amplitude were, in both cases, accompanied by clear indications of substantial increases in temporal dispersion as indicated by the very prolonged durations and 'multiphasic' character of the proximally evoked M potentials (figs. 7 and 8). In such cases enhanced temporal dispersion and phase cancellations among the component motor unit potentials could perhaps sufficiently reduce the compound M potentials

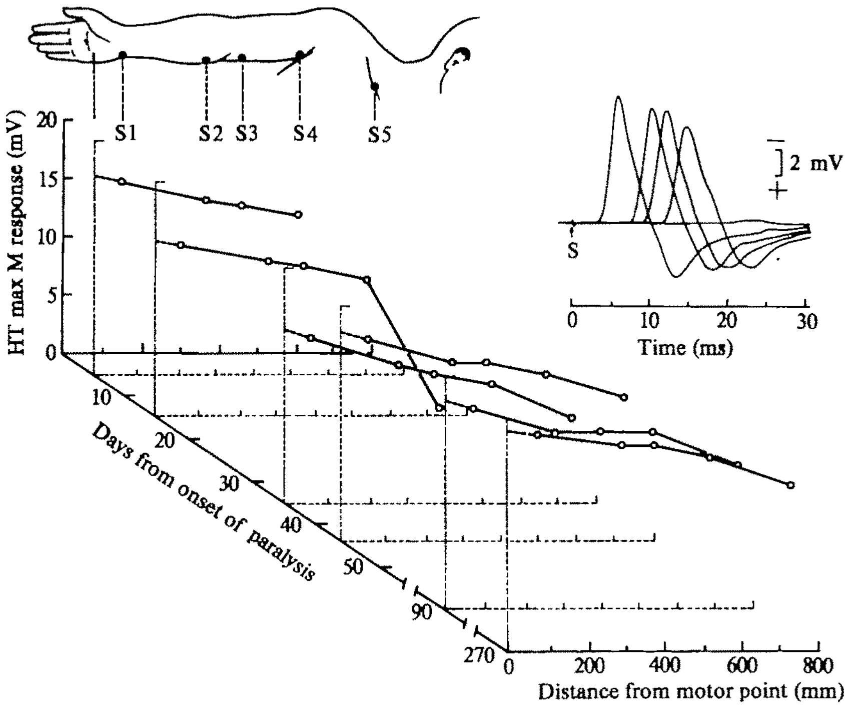

FIG. 6. A remarkable (more than 90%) reduction in the maximum hypothenar (HT) M potential as well as slowing of conduction between Erb's point and the upper arm in a patient with Guillain-Barré polyneuropathy examined fourteen days after the onset of the paralysis. The corresponding recorded potentials are shown in the *inset*. After another three weeks, these proximal conduction abnormalities had recovered. Here there was no increase in the p-p, −p, or total duration of the maximum M potential as elicited by stimulation at Erb's point in comparison with the equivalent potentials elicited by stimulation at more distal sites. The results of the studies at various times following the onset of the paralysis are shown.

to account for the changes in the M potentials as the distance between the site of stimulation and innervation zone in the extensor digitorum brevis increased. Such an alternative explanation to conduction block could account for the M potential reduction between the sciatic notch and popliteal fossa stimulation sites seen in fig. 7 but not those in fig. 8.

In the case illustrated by fig. 8, incremental stimulation at the levels of the lumbar roots and sciatic notch was able to elicit only 3 and 2 all or nothing EDB motor potentials, respectively. The thresholds of these motor axons at the two levels of stimulation were distinct and did not overlap. In contrast, the maximum M potentials elicited by stimulation at the levels of the fibular head and ankle were comprised of many more component motor unit potentials, the least estimates at the two respective levels of stimulation being 20 and 50 based on the incremental motor unit estimation technique (McComas *et al.*, 1971).

The above technique is of value in such instances in which the thresholds of all the motor axons are sufficiently distinct from one another that progressive increases in the stimulus intensity are able to reveal their presence by the successive all or nothing

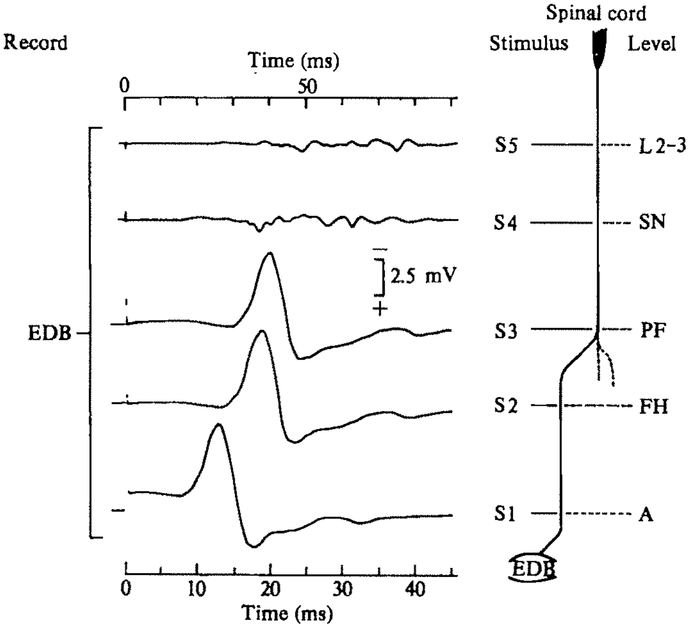

FIG. 7. Changes in the maximum M response in EDB on stimulation at the ankle (A), fibular head (FH), popliteal fossa (PF), sciatic notch (SN) and L2-3 roots. Here, even though there was an over 90 per cent reduction in the EDB M potential between the sciatic notch and popliteal fossa, this was accompanied by a doubling of the total duration of the M potential (note change in time scales). The latter indicated a substantial degree of temporal dispersion, especially between the popliteal fossa and sciatic notch stimulus sites. Maximum motor conduction velocity between LS-3 and the sciatic notch, the sciatic notch and fibular head, and the fibular head and ankle were 37, 46 and 42 m/s, respectively. The intermediate and proximal conduction velocities were well below the 2 SD lower limits of control subjects.

incremental increases to the M potential produced by the addition of single motor unit potentials, as the thresholds of their respective motor axons are exceeded in turn by the stimulus (figs. 5 and 8). In the two latter examples temporal dispersion and phase cancellations alone cannot account for the reductions in M potential amplitude at more proximal stimulus sites. Conduction block is a better explanation for such reductions.

Possible Distal Block

In this study the most distal sites of stimulation of the motor nerves were somewhere between 50 and 100 mm proximal to the innervation zones. Because of the possibility of transmission block in some motor axons beyond this site of

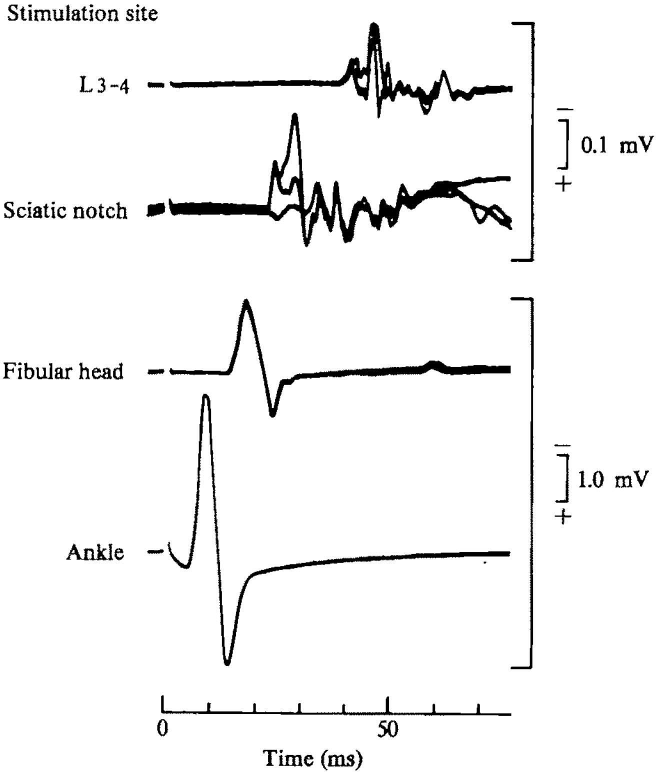

FIG. 8. Changes in the maximum M potential in EDB on stimulation at the ankle, fibular head, sciatic notch and L3-4 root levels. The p-p amplitude at the ankle was 60 per cent of the normal mean value in this muscle. The conduction block here is 'generalized' in its distribution, that is, conduction block was demonstrable across proximal, intermediate and more distal segments of these nerve fibres. Temporal dispersion, however, was especially evident in the asynchronous and dispersed EDB potentials elicited by stimulation at the sciatic notch and lumbar root levels. Even so, only 3 and 2 all or nothing motor potentials, respectively, could be identified by incremental stimulation at the respective root and sciatic notch stimulus sites. Maximum motor conduction velocity from L3 and 4 to the sciatic notch, the sciatic notch to the fibular head and the fibular head to ankle levels were 45, 36, 30 and 36 m/s, respectively. All these velocities were well below the 2 SD lower limits for control nerves. Note the gain in the upper two traces is ten times the gain in the lower two traces.

stimulation, the motor nerves were stimulated in some instances nearer to the innervation zone to establish whether the M potentials evoked by yet more distal sites of stimulation were indeed larger than those evoked by the more standard distal stimulation site. For both the peroneal and median nerves this proved to be true in a few cases; that is, stimulation progressively closer to the innervation zones led to progressive increases in the size of the M potential (fig. 9). Over the short distances of such studies, temporal dispersion and phase cancellations between component motor unit potentials probably have little or no effect on the size of the M potential which at these levels of stimulation probably bears a closer relationship to the numbers of excitable motor axons that remain.

Changes in Motor Conduction Velocity

The changes in motor conduction velocity are outlined in Table 1. It is clear that within the first fourteen days following the onset of paralysis, excluding the common

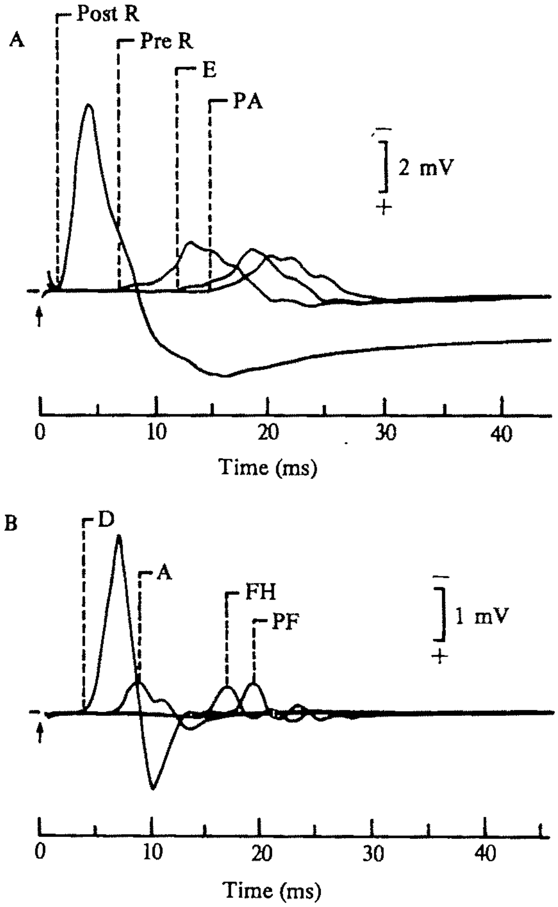

FIG. 9. Increases in the sizes of M potentials by stimulation nearer to the innervation zone than the usual sites for most distal stimulation, namely, the wrist or ankle. A, stimulation of the median nerve just distal to the flexor retinaculum (Post R), proximal to the retinaculum (Pre R), the elbow (E) and the proximal arm (PA) in a patient with Guillain-Barré polyneuropathy studied within two weeks of the onset of paralysis. Note the much larger M potential evoked by stimulation beyond the retinaculum, suggesting a very substantial degree of conduction block in the short segment of the median nerve lying beneath the retinaculum. B, stimulation of the peroneal nerve at the popliteal fossa (PF), fibular head (FH), and ankle (A), as well as at progressively shorter (20 mm) intervals (D) closer to the EDB innervation zone. Note the abrupt increase in the size of the EDB potential closer to the innervation zone, in this case possibly corresponding to the location of the extensor retinaculum beneath which the deep peroneal nerve must pass to reach EDB.

entrapment sites, maximum motor conduction velocity was within the normal range (−2 SD) in the majority, even in the peroneal nerve where the incidence of reduced conduction velocity was the highest (1/3) (*see* Table 1). After two weeks, slowing of motor conduction became more common, at least in the ulnar and peroneal nerves.

The incidence of these local conduction abnormalities at sites of entrapment were similarly common in the third and subsequent few weeks. In instances where the M potential amplitude was very low in response to distal stimulation, conduction across more proximal sites of entrapment, as at the elbow or fibular head, could not be adequately assessed. Such determinations were based on the few remaining motor axons still able to transmit their impulses through portions of the nerve distal to the entrapment.

There was no correlation between the presence or absence of disproportionate local conduction abnormalities at 'entrapment' sites, and the development or quantity of denervation in muscles in the distribution of these nerves. Fibrillation, when present, was never restricted to the territories of nerves in which these local conduction abnormalities were demonstrable.

TABLE 1. CHANGES IN MOTOR NERVE CONDUCTION VELOCITY

Ulnar nerve

Time following onset of paralysis (days)	*TML > 2 SD*	*MCV (BE–W) < 2 SD*	*Elbow segment*	*MCV (E–PA)*
1–14 (n = 15)	3	1	9	2
14–42 (n = 9)	3	3	4	2

Median nerve

	TML > 2 SD	*MCV (E–W)* < 2 SD	*MCV (E–PA)* < 2 SD
1–14 (n = 13)	9	1	1
14–42 (n = 4)	3	0	0

Peroneal nerve

	TML > 2 SD	*MCV (FH–A)* < 2 SD	*MCV (PF–FH)* < 2 SD
1–14 (n = 18)	2	6	10
14–42 (n = 7)	3	4	3

The values in the body of the Table are the numbers of nerves in each category. Abbreviations: TML = terminal motor latency; MCV = maximum motor nerve conduction velocity; BE–W = just below elbow (1–2 cm distal to cubital tunnel) to wrist; E–PA = Erb's point to proximal arm; E–W = elbow to wrist; E–PA = Erb's point to proximal arm; FH–A = fibular head to ankle; PF–FH = popliteal fossa to fibular head.

Conduction Across Common Entrapment Sites

Even in the early period (one to fourteen days) disproportionate slowing of motor conduction (more than 20% compared to adjacent segments) was evident across the common entrapment sites. For example, slowing of conduction in excess of that proximal or distal to the elbow segment (which includes the retroepicondylar and cubital tunnel segments) was present in 60 per cent of the ulnar nerves tested. Likewise in the peroneal nerve the frequency of such excessive conduction slowing across the fibular head was high (56%). In about a half of these instances, conduction slowing at the 'entrapment' site was accompanied by disproportionate conduction block (more than 20% compared to adjacent segments).

In the median nerve, the presence of focal conduction slowing beneath the flexor retinaculum was suggested by the presence of prolonged terminal motor latencies in 69 per cent (first two weeks) of the median nerves while in only 20 per cent of ulnar nerves were there corresponding prolongations of the terminal latency.

Changes in M Potential Size

In the first fourteen days, the amplitude of the maximum M potential as elicited by stimulation at wrist or ankle level were often already below the 2 SD lower limit for controls and in most proceeded to decline further before recovering, usually after three to four weeks (fig. 10). That some of the initial M potential amplitudes were

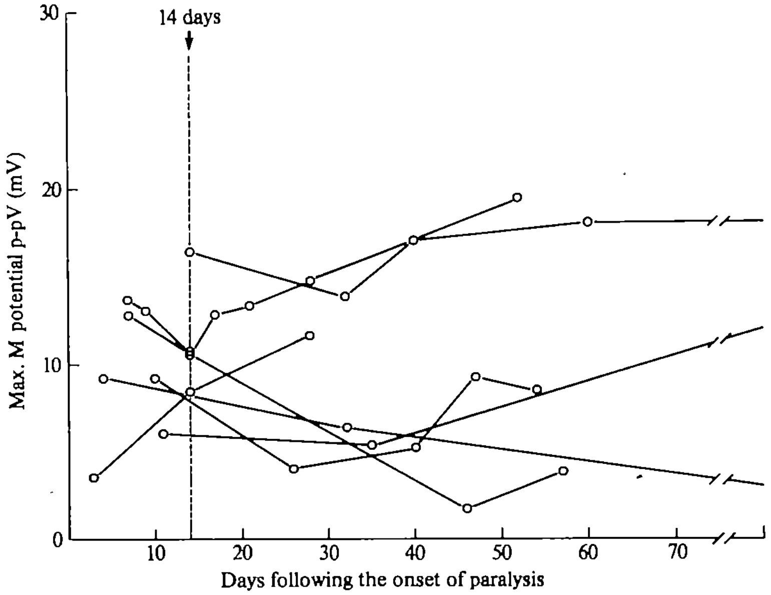

FIG. 10. Plot of changes in the p-p amplitude of the hypothenar M potential at various times following the onset of paralysis. Values beyond ninety days are shown for 3 subjects beyond the interrupted x axis. Note the decline in the amplitudes of the M potentials in most patients over the first few weeks and the subsequent recovery in some. The 2 SD lower limit of the hypothenar maximum potential is 13.5 mV.

depressed at the time of the first examination even though the value was within the 2 SD lower limit of controls, was suggested by the finding that at later follow-up (six months or more) the amplitude was 20 to 30 per cent higher.

Incidence of Denervation

There was a good correlation between the amplitude of the maximum M potential to the most distal site of stimulation as assessed at the initial examination and the subsequent development and degree of denervation in the target muscles (Table 2).

TABLE 2. AMOUNT OF FIBRILLATION IN RELATION TO THE AMPLITUDES OF THE MAXIMUM M POTENTIALS

*Amplitude of the maximum M potential**	*Amount of fibrillation*				
	0	+/−	+	++	+++
> 50	3	—	1	1	—
51–80	3	—	—	—	—
26–50	1	1	—	2	—
10–25	—	2	2	—	—
< 10	—	1	—	1	5

The values in the body of the Table are the numbers of muscles (thenar, hypothenar and EDB) where correlations were possible between the amplitudes (p-p) of the maximum M potentials within the first two weeks following the onset of the paralysis and the amount of fibrillation subsequently seen in the respective muscles. *Expressed as a percentage of the mean control maximum M potential amplitude.

Thus where the maximum M potential amplitude exceeded 50 per cent of the control mean values, denervation subsequently developed in only about 20 per cent of the thenar, hypothenar or EDB muscles. However, where the amplitudes of the M potential were less than 50 per cent of the respective control mean values, denervation was later seen in 93 per cent of the muscles. Fibrillation was very common (+ + +) in those muscles where the amplitude of the maximum M potential was below 10 per cent of the normal mean values. In the latter group, axonal degeneration must have developed in at least some of the preterminal or terminal motor axons. However, not all muscles where the amplitudes of the maximum M potentials were reduced (< 2 SD below the normal mean) went on to develop more than a few fibrillation potentials, while in others no fibrillation potentials developed in subsequent studies.

Overall, denervation was demonstrable in one or more of the index muscles in 64 per cent of the patients, and was more common in distal than in proximal muscles, and in lower limb than in upper limb muscles. The earliest time at which denervation became evident was nine days following the onset of the weakness. In most patients, however, fibrillation was not seen until the third or fourth weeks of the weakness.

Clinical Outcome

The clinical outcome correlated with the amplitudes of the initially recorded maximum M potentials. Only 8 of 26 Groups I and II muscles (initial M response $> 10\%$ control mean) were wasted, whereas 6 of 7 Group III muscles were wasted at follow-up. In Group I (initial M potential $> 50\%$ control mean; $r = 6$) the mean recovery grade at follow-up was 1.5, whereas the mean in Group II (initial M potential 10 to 50% control mean; $n = 7$) was 2.0 and in Group III (initial M response $< 10\%$ control mean; $n = 4$), 2.75. Even though the numbers of patients are small there was a significant difference ($P < 0.05$) between the clinical grades of patients in Group III compared with patients in Groups I and II taken together, although not between Groups I and II.

DISCUSSION

Conduction block, low distal M response amplitudes or both were present in one or more motor nerves in 74 per cent of GBS patients within two weeks of the onset of the paralysis. In contrast, overall maximum motor conduction velocity was below the 2 SD lower limit of control mean values in a little less than one fifth of motor nerves (6:46) and the terminal motor latencies longer than normal in about one third (14:46) in the same period. Abnormal temporal dispersion was present in less than 20 per cent of the M responses. Conduction block, low amplitude M responses, or both, are therefore much more characteristic in the earliest weeks of the disease than is slow motor conduction velocity.

The majority of motor unit potentials as recorded with a surface stigmatic electrode positioned over the innervation zone are biphasic (negative positive). Hence degrees of temporal dispersion among component motor unit potentials in the compound M potential such that opposite phases overlap can result in appreciable reductions in the area of the M potential. The effect is to add further to whatever reductions in amplitude occur simply through the effects of temporal dispersion alone. However, from computer simulation studies in this laboratory of the effects of temporal dispersion and phase cancellation on the amplitude, duration and area of the M potential, it is clear that reductions in amplitude in excess of normal values when unaccompanied by any increases in duration (peak, peak to peak or total) beyond that seen in normal subjects, are explained by conduction block and not by temporal dispersion and interpotential phase cancellations. In any case, in about three quarters of the motor nerves where conduction block was judged to be present, the reduction in amplitude exceeded 50 per cent and was unaccompanied by any significant increase in duration (−p or p-p). Total durations of the M potentials were not included since this can be very difficult to measure accurately because of the slow time course of the terminal positive phase and the superimpositions of late waves on this potential. At the limit, where only a few motor axons remained excitable, conduction block in one or more of these axons could readily be recognized despite substantial degrees of temporal dispersion being apparent in the summation of the respective maximum M potential.

In the presence of very low amplitude M potentials, it is usually impossible to assess conduction block adequately proximal to the most distal sites of stimulation. The true frequency of instances where conduction block in the most proximal segments of the peripheral nervous system exceeded the degree of block in more peripheral segments was difficult to judge. Reasons for this included the inability to measure conduction block between the cervical cord and Erb's point in the upper limb, and the natural hesitation, despite its apparent safety, of measuring conduction across the lumbosacral roots and plexus by near root stimulation techniques in all patients. Despite these inherent problems, degrees of conduction block obviously in excess of those across more distal segments were seen in two ulnar nerves between Erb's point and the proximal arm stimulation sites. In one of these nerves, the proximal block had reversed by the time of the next examination.

In the two instances where lumbar root and sciatic nerve stimulation was undertaken, conduction block was demonstrable in one instance proximal to knee level. The latter is usually the most proximal stimulation site in conventional motor conduction studies of the peroneal and tibial nerves.

Low M potential amplitudes to distal stimulation could reflect primary demyelination and conduction block between the site of stimulation and the innervation zone. Alternatively, conduction block in axons undergoing axonal degeneration (Erlanger and Schoepfle, 1946), or the loss of motor axons prior to the test, could also contribute to the low M response amplitudes. Unfortunately the quantitative extent to which motor axons have been lost through axonal degeneration cannot be measured by current electrophysiological techniques, although once denervation in the muscle develops, some estimate of the degree of axonal degeneration may be made from the numbers of fibrillating muscle fibres in the muscle.

Fibrillation was indeed more common in muscle groups where the amplitude of the maximum M potential was below 50 per cent of the control mean value, and was especially common where these amplitudes were below 10 per cent of the mean values. These observations and the persistence in some cases of low M potentials over the next few weeks and months are strong evidence that at least some proportion of the motor axon population had undergone degeneration of wallerian type. Even in those instances where the amplitudes of the M response exceeded 50 per cent of the control mean values, some denervation activity was seen in about 20 per cent of the muscles. Moreover, patients with the very low maximum M amplitudes in the acute paralytic stage were also the most likely to demonstrate weakness and wasting in the muscle groups studied in this investigation and, more importantly, subsequently to develop the most extensive and severe residual motor disabilities.

Low amplitude maximum M potentials may not always be due to degeneration of entire axons but could indicate the presence of demyelination, axonal degeneration or both in the terminal arborization of the motor axons beyond the most distal stimulation site. Lesions have been found in the terminal motor twigs (Asbury *et al.*, 1969) but they may be underestimated because they are difficult to quantitate. Humoral demyelinating factors (Feasby *et al.*, 1982) could gain access to these distal nerve twigs since the perineurial barrier is deficient at the peripheral end of motor axons (Burkel, 1967). Rapid repair of terminal axonal degeneration or demyelination by axonal regeneration or remyelination respectively could explain those instances of surprising recovery in spite of low maximum M responses in the acute stage.

The presence of normal or near normal maximum conduction velocities in the early period when conduction block is well established suggests that the fastest conducting motor axons are often not among those whose impulses are blocked. Indeed, it is possible that the earliest motor axons to be blocked are the slower conducting axons in view of the recent experimental evidence (Lafontaine *et al.*, 1982).

Experimental demonstration of conduction block producing transient loss of function was first correlated with demyelination by Denny-Brown and Brenner (1944) in compressed nerves, and in diphtheritic neuropathy by McDonald (1963). Subsequent studies (reviewed in Sears and Bostock, 1981) have shown conduction block to be one of the most important physiological consequences of demyelination. It is a prominent characteristic of experimental allergic neuritis (EAN), a possible experimental model of the GBS (Kaeser and Lambert, 1962; Cragg and Thomas, 1964).

Demyelination and conduction block may be caused by humoral factors in both EAN and the GBS. Demyelination can be produced by the intraneural injection of rabbit EAN serum (Saida *et al.*, 1978; Hahn *et al.*, 1980), probably by antibody against a component of myelin, possibly galactocerebroside (Saida *et al.*, 1979). Antigalactocerebroside antibody rapidly produces conduction block when applied to rat ventral nerve roots (Lafontaine *et al.*, 1982). Conduction block is associated with a marked increase in nodal capacitance, probably due to acute paranodal demyelination (Brown *et al.*, 1980). Sumner *et al.* (1982) have shown that conduction block develops over several days in rat nerves injected with GBS serum. This correlates with the observation that slowly evolving demyelination develops in rat nerves injected with GBS serum (Feasby *et al.*, 1982).

Demyelination and axonal degeneration are both present in EAN (Lampert, 1969) and the GBS (Asbury *et al.*, 1969). The precise relationship between these two morphological abnormalities is uncertain. Madrid and Wiśniewski (1977) suggested that axons could be damaged in a nonspecific manner by the inflammatory process, but whether this is the sole explanation of the changes in axons is unknown.

Slowing of conduction and increased temporal dispersion among impulses in different motor nerve fibres would not by themselves be expected to cause paralysis provided transmission of impulses was not interrupted in the main axon or the distal arborization. Neither of these abnormalities was common in our patients when studied early in the disease when paralysis was most severe. Experimental studies of a synchronously demyelinating lesion have shown that significant slowing of conduction velocity and temporal dispersion are not present in axons undergoing demyelination prior to conduction block, but develop later in the recovery phase (Smith and Hall, 1980).

Very slow motor conduction velocities are quite compatible with normal strength as in the type I hereditary motor and sensory neuropathy (Dyck and Lambert, 1968). Slowing of conduction and increased temporal dispersion could, however, impair those physiological activities which are dependent on a high degree of synchronization in the transmission of their peripheral afferent impulses, as in the appreciation of vibration sense and tendon reflex responses.

Frequency-dependent conduction block theoretically could produce weakness by interrupting the transmission of impulses in motor axons. Indeed, an increased refractory period of transmission (RPT) has been demonstrated in experimental demyelination (McDonald and Sears, 1970; Rasminsky and Sears, 1972; Smith and Hall, 1980). Such critical interimpulse intervals as have been described, however, would be too short (< 5 ms) compared to the maximum discharge frequencies of human motor units (25 to 50 Hz) to cause frequency-dependent block. Possibly a higher RPT is present in the much smaller diameter terminal and preterminal motor branches. Moreover, doublet discharges of motor units, a mechanism for producing a 'catch like' increment in force, could clearly be impaired if the RPT were increased (Burke, 1980).

The disproportionate conduction abnormalities observed at common entrapment sites are possibly explained by the natural liability to compression injuries of these nerves at these relatively exposed sites in patients unable to move their limbs. Their occurrence stresses the importance of careful attention to these sites by cushioning, beginning as early as possible in the illness. Whether the nerves in the GBS are any more vulnerable to physical trauma because of the polyneuritis is unknown, but such a mechanism has been postulated to contribute to the compression neuropathies in guinea pigs with experimental diphtheritic neuropathy (Hopkins and Morgan-Hughes, 1969).

We conclude that the acute paralysis in the GBS is mainly due to conduction block resulting from primary demyelination. Axonal degeneration makes a variable contribution to the acute paralysis but seems to be the main cause of residual muscle weakness or wasting. The amplitude of the M potentials as recorded early following the onset of the paralysis does correlate with the subsequent development of denervation, at least in distal muscle groups. Clinical recovery, however, is more often judged from the actions of the larger proximal muscle groups, such as the trunk, proximal limb and bulbar muscles, the more distal muscles, such as those chiefly studied here, being less important. Despite this, in our study there was a good correlation between the amplitudes of the maximum M potentials in the distal muscles and not only the subsequent development of denervation, but also the clinical outcome.

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THE RELATIONSHIP BETWEEN THE EVOKED POTENTIAL AND BRAIN EVENTS IN SENSORY DISCRIMINATION AND MOTOR RESPONSE

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SUMMARY

The relationship between the various components of the cerebral evoked potential, sensory discrimination and the initiation of motor responses is controversial. In order to study this relationship, we recorded long-latency evoked potentials from the scalp together with the EMG in a reaction time experiment where the subject was required to make a motor response to one of two auditory stimuli. The peak latencies of event-related components were all found to correlate with EMG response times. Similar results have been reported by others and have led to suggestions that one or another of these components reflects electrical activity in neural structures that are responsible for sensory discrimination. In our experiments, however, the EMG response generally preceded all these components. This observation, whether it relates to the simplicity of our task, the use of EMG to measure reaction time, or to some combination of these factors, implies that these event-related potentials cannot reflect cortical events involved in either sensory discrimination or the initiation of a motor response. Presumably these components must reflect subsequent neural events in the processing of infrequent target tones.

INTRODUCTION

There has recently been considerable interest in the relationship between the cortical response accompanying information processing, the timing of mental processes such as sensory discrimination and perception, and the timing of a motor response. In many studies attention has been directed particularly at the 'event-related' components of the evoked potential. These components, unlike the 'stimulus-related' components, are relatively insensitive to the physical characteristics of the eliciting stimulus such as intensity, pitch and duration, but depend primarily upon the context in which the stimulus occurs. Thus they generally require the subject to attend to the stimulus and distinguish it from similar nontarget stimuli, and are influenced both by the difficulty of the sensory discrimination and the probability of occurrence of the target stimulus (*see* Donchin *et al.*, 1978, and Tueting, 1978, for

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reviews). One of these event-related components is a positive potential (relative to a prestimulus baseline) which is recorded at the vertex approximately 300 ms after a stimulus and which has been designated P300 or P3. Several studies have shown a positive correlation between the latency of this component of this event-related potential and reaction time (Ritter *et al.*, 1972; Kutas *et al.*, 1977; Roth *et al.*, 1978; McCarthy and Donchin, 1981; Duncan-Johnson, 1981). Because the motor response usually follows the P3 latency, there has been considerable speculation as to the possible role of P3 in sensory discrimination.

Some authors have noted, however, that on occasion the reaction time is shorter than the P3 latency (Ritter *et al.*, 1972, 1979; Renault *et al.*, 1982), suggesting that earlier event-related components may represent the electrical concomitant of sensory discrimination. Indeed, Ritter *et al.* (1979) showed that the preceding negative (N2) peak latency was correlated with reaction time and suggested that 'the brain events underlying N2 are responsible for, and initiate in parallel, the neural activity related to relevant motor responses and the processes reflected by P3'. In a recent study by Renault *et al.* (1982), a central and parietal N2 were distinguished in a visual omitted-stimulus experiment, and it was suggested that the parietal N2 onset was associated with the detection of the omitted stimulus.

In all these experiments the reaction time was assessed by the movement of a finger through a certain distance or by switch closure, rather than by electromyography (EMG). Since EMG onset precedes movement and is less dependent on mechanical variables, the relationship between cerebral processes and motor activity can be better defined if the EMG is used as a means of monitoring motor activity. Accordingly, in order to delineate more clearly the relationship between the reaction time and the various event-related components of the evoked potential, we used EMG onset in a simple choice reaction time experiment where the subject was required to make a motor response to one of two stimuli.

METHODS

Fourteen adult subjects (aged 25 to 40 yrs) participated in this study. Each subject was presented binaurally with a predetermined sequence of 420 tones (65 dB HL, 50 ms duration) at a rate of one tone every 1.5 s. The tones were of two different pitches. The frequent tone had a frequency of 1000 Hz and occurred in 86 per cent of the trials, while the rare tone had a frequency of 2000 Hz and occurred in 14 per cent of the trials. The sequence was pseudorandom, with the constraint that no two rare tones occurred consecutively. Subjects were asked to perform three separate tasks. In the first (Attend-React) task the subject was instructed to extend his right middle finger as quickly as possible after he detected a rare tone. In the second (Attend-Count) task the subject was asked to keep a mental record of the number of rare tones but instructed not to react to them. In the third (Ignore) task the subject was instructed to ignore the tones and concentrate instead on reading a magazine of his choice. The cerebral responses to the frequent and rare tones were recorded from Fz, Cz and Pz electrode placements on the scalp (international 10:20 system), with reference to linked mastoids, and averaged using a Nicolet Pathfinder II system (bandpass 1 to 40 Hz). The EMG was recorded from an active electrode situated over the motor point of the extensor digitorum for the middle finger, with a reference electrode placed over the muscle tendon in the ipsilateral hand. Small movements of one finger were used because such movements are said to be associated with minimal premotor potentials (Ritter *et al.*, 1972, 1979; Renault *et al.*, 1982).

In 9 of the subjects the individual responses were also examined. Because of computer limitations, however, the probability of the rare tone occurrence was reduced from 14 per cent to 9 per cent in these single trial recordings.

Peak latencies were measured by extrapolating lines from the ascending and descending portions of a wave, and measuring the latency at the point of intersection. Onset of a particular component was measured from the peak of the preceding component. Eye movements were monitored from electrodes placed supraorbitally and at the outer canthus of the left eye. No systematic eye movement potentials were seen.

RESULTS

The vertex (Cz) evoked potential waveforms for one of the subjects are shown in fig. 1. Since there were no consistent differences between the waveforms obtained in the Attend-React and Attend-Count conditions, only the former will be discussed.

In response to the frequent tone in both the Attend-React and the Ignore conditions, and to the rare tone in the Ignore condition, a characteristic negative (N1)-positive (P2) complex was obtained. To the rare tone in both the Attend-React

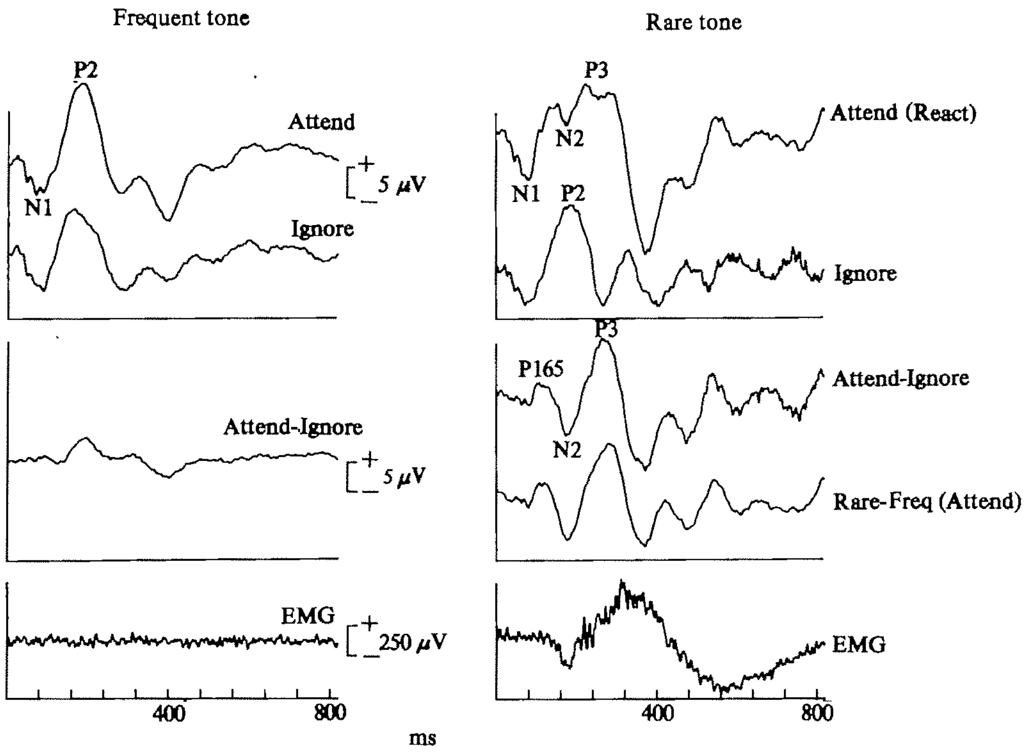

FIG. 1. Vertex evoked potential waveforms for a single subject. The top two traces for both the frequent and rare tones are those obtained in the Attend-React and the Ignore conditions, the middle traces are difference waveforms derived by subtraction techniques (*see* text), and the lower traces are the averaged EMG responses.

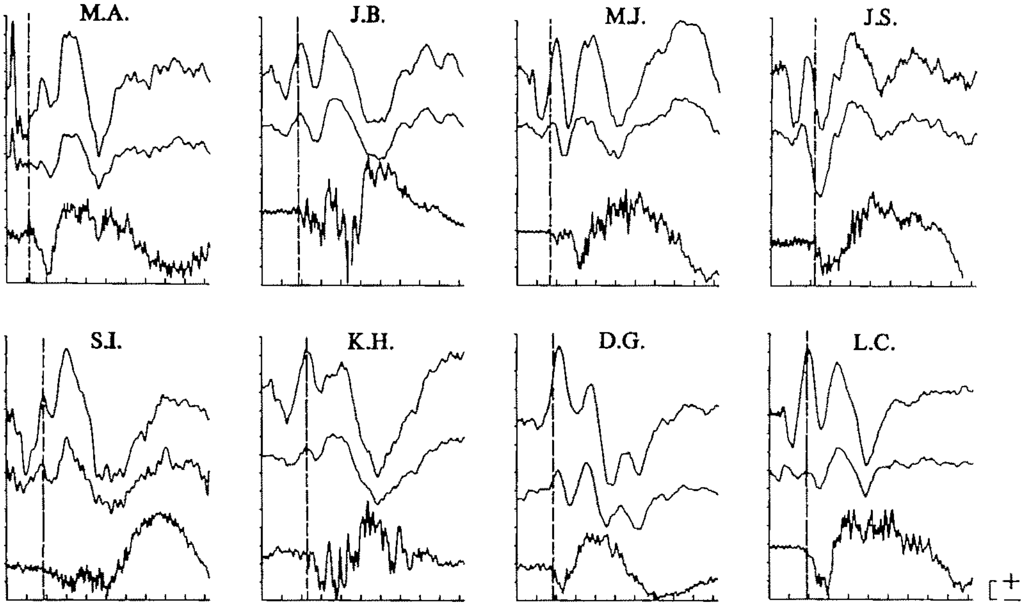

FIG. 2. Evoked potential waveforms from 8 subjects. The top trace for each subject is the waveform for the rare tone in the Attend-React condition. The middle trace is the difference waveform obtained by subtraction of the frequent tone waveform from the rare tone waveform in the Attend-React condition. The dotted line represents the onset of the averaged EMG response, shown in the lower trace. The abscissa represents time (80 ms/division). The calibration sign represents 5 μV for the cortical evoked potentials and 250 μV for the averaged EMG.

and the Attend-Count conditions, however, a considerably more complex waveform was produced. In addition to the N1 component, there was a P2 of slightly earlier latency than the Ignore P2 (termed 'apparent P2' because of its earlier latency), followed by a small negative deflection (N2), and then a large positive deflection (P3). From these four 'basic' waveforms, difference waveforms were constructed by digital subtraction of the Ignore waveform for each tone from the corresponding Attend-React waveform. Under these stimulus conditions there were no consistent differences between the frequent tone Attend and Ignore waveforms (Goodin *et al.*, 1978*a*) and consequently our frequent tone difference waveforms were essentially flat lines. The rare tone difference waveform, however, showed a characteristic positive (P165)-negative (N2)-positive (P3) complex reported previously (Goodin *et al.*, 1978*b*). This P165-N2-P3 complex was also obtained by the digital subtraction of the frequent tone waveform from the rare tone waveform in the Attend-React condition. As shown in fig. 1, this complex was the same irrespective of which subtraction procedure was used to derive it, and so the latter was used to obtain the peak and onset latencies reported below. The last waveforms shown in fig. 1 are the averaged EMG responses in the Attend-React condition. The averaged EMG response to the frequent tone was a flat line since the subject was not required to react to this tone, while the averaged EMG response to the rare tone consisted of a well-formed negative-positive complex reflecting finger extension by the subject. Performance on this task was highly accurate. No subject made more than two commission errors (error rate < 0.5 per cent) and none made any omission errors.

Fig. 2 shows the averaged data from 8 additional subjects. The dotted lines indicate the onset of the averaged EMG response. In all but subject J.S., the averaged EMG onset either precedes or is coincident with both the peak of the apparent P2 seen in the Attend-React waveform (top trace) and the peak of P165 seen in the difference waveform for each subject (middle trace). This result is also seen in the Table which lists the average peak latencies and the average reaction time for all 14 subjects. The Table shows that of all of the event-related components (P165, N2 and P3), only the onset of the P165 preceded the onset of the averaged EMG activity.

In order to define the basis of the averaged EMG, we also examined single trial

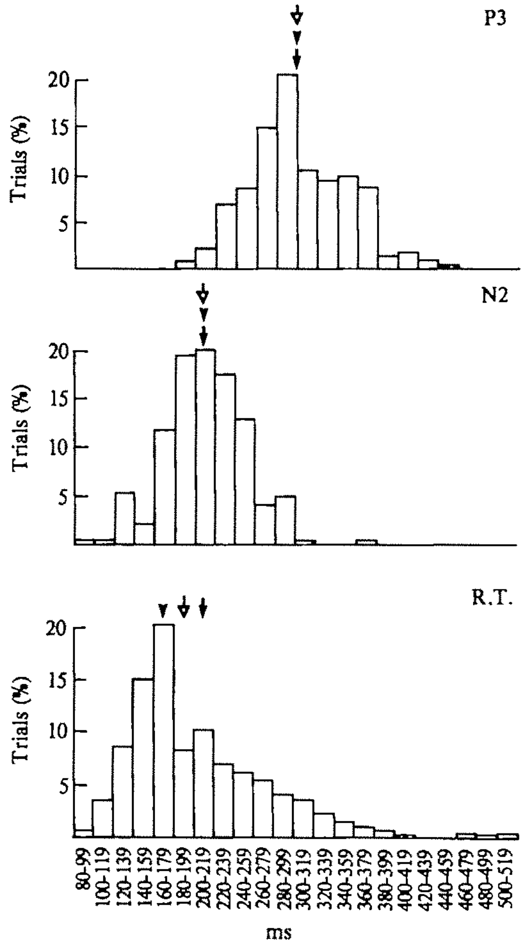

FIG. 3. Frequency histograms for the single trial reaction time (RT), N2 and P3 latencies. Small arrows indicate the arithmetic mean and the open arrows indicate the median of the distributions. The arrowheads indicate the mean latency of the averaged responses (determined from the Table). The N2 and P3 latencies are normally distributed whereas the reaction times are skewed to earlier responses. The latency of onset of the averaged EMG (RT) occurs at about the 25th percentile.

TABLE. EVOKED POTENTIAL COMPONENTS AND REACTION TIME

Component	*Mean latency (ms)*[a]	*Mean latency difference (ms)*[b]	*Slope of latency vs RT regression line (RT on x-axis)*
N1	90 ± 8	−2 ± 9[c]	—
P2	169 ± 16	3 ± 17[c]	—
P165	155 ± 22	2 ± 7[c]	0.84[e]
Onset P165	115 ± 22	0 ± 17[c]	—
Apparent P2	164 ± 12	−2 ± 15[c]	—
N2	214 ± 28	1 ± 7[c]	0.13[f]
P3	297 ± 23	0 ± 17[c]	0.28[f]
RT	155 ± 33	19 ± 26[d]	—

[a] Data from all 14 subjects. The probability of rare tone occurrence was 14%. [b] Difference in mean latency between averaged responses to rare tones occurring with a probability of 14% and 9% in 9 subjects. (Minus symbol indicates that the latency in the 14% condition was longer.) [c] Not significant, using paired t-test. [d] $P < 0.05$, using paired t-test. This does not take into consideration the skewed nature of the RT distribution. [e] Slope of P165 regression line in a single subject. The data was sorted into RT bins of 10 ms and average waveforms computed for each bin. From each of these averaged waveforms an ignore waveform was subtracted and the P165 latency assessed from these difference waveforms. These P165 latencies were then correlated with the average RT for each bin ($P < 0.001$). [f] Single trial data from all 9 subjects ($P < 0.001$).

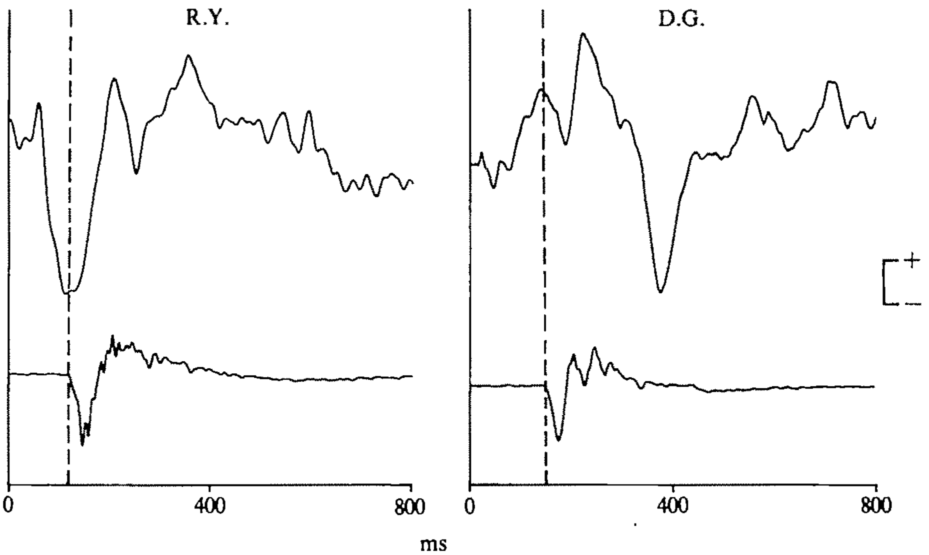

FIG. 4. Averaged evoked cerebral responses (*top trace*) in 2 subjects for a restricted range of reaction times, the average of which is shown in the *bottom trace*. For subject R.Y. reaction times ranged between 116 ms and 126 ms, whereas for subject D.G. it ranged between 140 ms and 155 ms. Calibration sign represents 10 μV for the cortical evoked potential and 250 μV for the EMG.

recordings in 9 subjects. The relationship between onset of the averaged EMG and the distribution of single trial EMG onsets (reaction times) for all 9 subjects is depicted in fig. 3, together with the distributions of the N2 and P3 peak latencies. The N2 and P3 components are distributed normally while the reaction time distribution is clearly skewed to earlier responses. We therefore also examined the relationship between the averaged cerebral response and the EMG findings in 2 subjects, each of whom was studied repeatedly so that they had a number of EMG responses occurring early and within a very restricted latency range. The cerebral responses occurring in these trials were averaged for each subject, and the results are shown in fig. 4. This analysis results in an evoked response that is time-locked both to tone onset and to movement, and again it can be seen that the EMG activity commences at or before the apparent P2 latency.

Fig. 5 shows 11 of the single trial EEG and EMG responses from one subject in

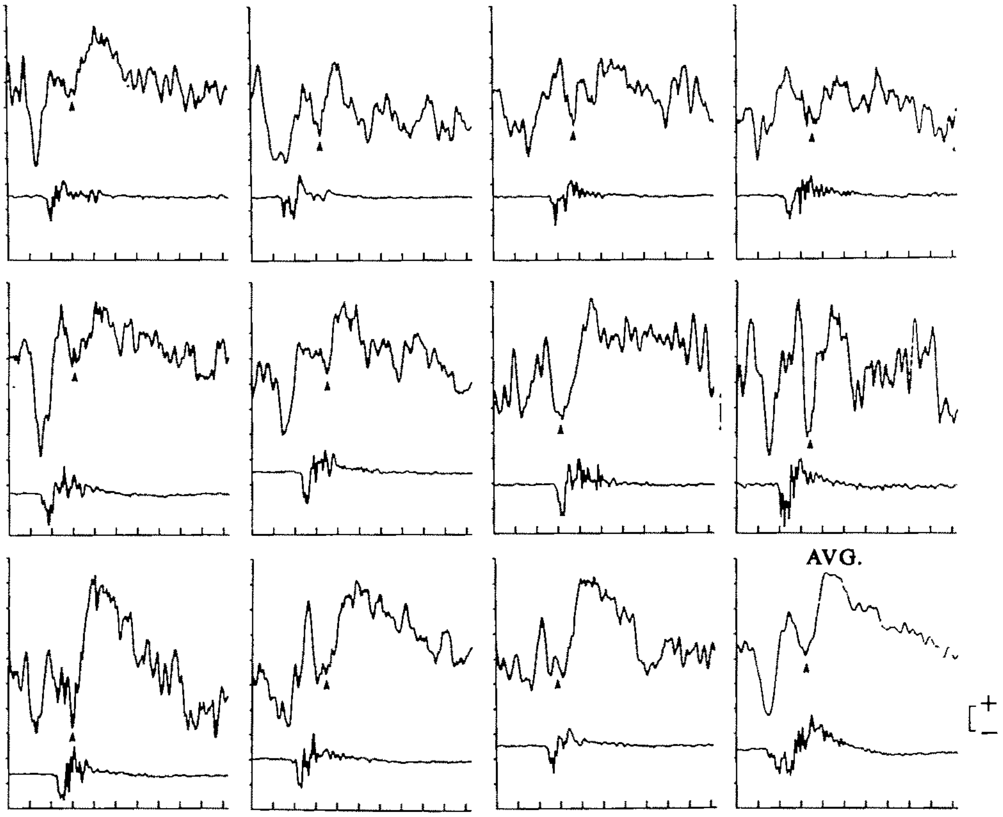

FIG. 5. Single trial responses from one subject. The *top traces* are the single trial EEG responses, and the *lower traces* are the EMG responses to the same rare tone presentation. The arrowheads represent the latency of the N2 component as evaluated from each single trial. The traces shown in the lower right panel represent the average (AVG) of these 11 single trials. In each single trial a negative-positive-negative-positive complex can be identified which presumably represents the N1-apparent P2-N2-P3 complex for each trial. Time is represented on the abscissa (80 ms/division). The calibration sign represents 10 μV for the cortical evoked potential and 250 μV for the EMG.

addition to the average for these 11 trials. For the earliest reaction times in all 9 subjects the EMG onset occurred before the apparent P2 (9/11 in this figure), while for the longest reaction times the EMG onset usually followed the N2 peak latency and occasionally followed the P3 peak latency. Since P165 can only be identified from subtracted waveforms, one subject was further evaluated with a large number of single trial recordings in both Attend and Ignore conditions so that the relationship between this peak and the reaction time could also be investigated. Consistent with previous reports (Ritter *et al.*, 1972; Kutas *et al.*, 1977; Ritter *et al.*, 1979; Renault and Lesevre, 1979; Duncan-Johnson, 1981), the peak latencies of the P165, N2 and P3 components were all significantly correlated with the reaction time (*see* Table).

DISCUSSION

A comparison of the onset of the averaged EMG should properly be made with the onset, rather than the peak, of an averaged cerebral component. This is because the variation in single trial latencies for both the EMG and cerebral components exceeds their duration (figs. 3, 4 and 5), and each average component onset will therefore reflect only the faster responses. Indeed, the onset of the averaged EMG generally occurred at about the 25th percentile (fig. 3) and thus reflects an average of the fastest half of the motor responses. Averaged component peaks, in contrast, reflect all the responses, and thus the measured peak latency corresponds to the mean of all the single trial peak latencies (fig. 3). The only difference between the cerebral response and the EMG response is that the onset of the former can be less reliably determined because of the overlapping of positive and negative components and because of a smaller signal to noise ratio.

The skewed nature of the reaction time distribution and the gaussian nature of the cerebral peak latency distributions (fig. 3) suggests, however, that even a comparison of onset to onset may not be completely symmetrical. The reaction time distribution is skewed to earlier responses, and the onset of the averaged EMG should therefore reflect a larger proportion of the responses than the onset of an averaged cerebral component. The bias introduced by this comparison should then produce a relative shortening in the latency of the onset of an average cerebral component. Despite this, we found that all of the event-related components except P165 had their onset after that of the averaged EMG.

To further establish the validity of this observation, we undertook two other analytical approaches. First, we examined single trial EEG and EMG responses. Since the onset of a cerebral component could not be established in single trials, we were forced to compare EMG onset to cerebral peak. Nevertheless, EMG onset frequently occurred at or before apparent P2 peak latency (fig. 5), according fully with our conclusions from the averaged data. Secondly, in 2 subjects we averaged only those single trial cerebral responses in which the EMG onset occurred at the same latency after tone onset (fig. 4). This method of analysis results in an averaged cerebral response that is time-locked both to the stimulus and to the motor response. This latter analysis is, perhaps, the most persuasive evidence that an accurate motor response can precede all of the event-related components. Since the motor response is effectively synchronous, the averaged EMG reflects all responses, whereas the variability of the individual cerebral responses (greater than 60 ms in these single trials) assures that onset of the averaged response will, as discussed above, reflect only the faster ones. Despite this bias, the findings unequivocally support our conclusions.

In considering these findings, the delay that exists between the cortical event that initiates a motor response and the onset of the resulting EMG activity or movement must be borne in mind. The duration of this delay is uncertain but presumably depends, in part, upon which muscle responds. Ritter *et al.* (1972) estimated that for responding upper extremity muscles this delay is approximately 45 ms. Such a figure is compatible with the finding by Evarts and Fromm (1978) that pyramidal tract neurons in the monkey become active approximately 60 ms prior to EMG activity in responding wrist extensors and the recent report by Merton *et al.* (1982) that electrical stimulation of the human motor cortex produces a response in adductor pollicis after a latency of 23 ms. If a delay of 25 to 60 ms is held to apply in human subjects, then the conclusions to be drawn from our experimental results seem clear. The mean onset of the averaged EMGs was 155 ms after the stimulus, and any cortical evoked potential component directly related to genesis of the motor response should therefore occur at or before a latency of 95 to 130 ms, while any component related to the sensory discrimination preceding the cortical initiation of a response should occur even earlier. Both the N2 and P3 components are clearly too late to have any causal relationship to the motor response. The only component of the event-related potential that even approaches this latency range is the P165, which has an average onset of 115 ms. However, since P165 is present to rare tones regardless of whether or not there is a motor response (Goodin *et al.*, 1978*a*), it cannot reflect activity in neural structures that directly initiates the response. Moreover, even this component probably does not occur early enough to relate to sensory discrimination. Consequently, at least for our experimental conditions, the entire sequence of event-related components must follow any neural events that lead to the motor response. Our observed correlations of reaction time and peak latency (*see* Table), then, presumably reflect the initiation in parallel of both the event-related response and the motor response by a prior neural event.

Our measured reaction times are considerably shorter than those of other authors under choice reaction time conditions. This may relate to a difference in experimental design. We measured the reaction time by the onset of EMG activity whereas others have used either finger motion or switch closure. In order to determine whether this explained the discrepancy, we measured the difference between finger movement (as indicated by an accelerometer) and EMG onset in one of our subjects, and found a difference of 40 ± 5 ms. This result is consistent with that reported earlier by Ritter *et al.* (1972), but is nevertheless insufficient to explain the large differences in reaction times reported. Another difference between our study and those of others is in the simplicity of our task. Our stimuli occurred at predictable intervals and the only uncertainty for the subject was which of two easily discriminable stimuli had been presented.

While this may account for our reaction times being so short, it does not explain why our reaction times were consistently earlier than the latency of the entire event-related response while other authors report reaction times that are longer than the latency of at least part, if not all, of this response (Ritter *et al.*, 1972; Kutas *et al.*, 1977; Roth *et al.*, 1978; Ritter *et al.*, 1979; McCarthy and Donchin, 1981; Duncan-Johnson, 1981; Renault *et al.*, 1982). This apparent conflict may relate to the slopes of the latency *vs* reaction time regression lines, all of which are considerably less than one (*see* Table). This conforms to the findings in the previous reports cited above, in which the relative changes of reaction time and peak latency are either given or can be calculated from the data. Since it has been well established that the latencies of the event-related components are significantly affected by changes in task difficulty, the implication of this observation is that the motor response is disproportionately delayed by increased task demands. Thus, in very simple tasks the motor response may precede the entire event-related response, while in harder tasks the motor response may follow it.

These results suggest three possible conclusions about the neural organization responsible for sensory discrimination and the initiation of a motor response. First, there may be no single component of the cerebral evoked potential that reflects sensory discrimination. In this view the motor response would be triggered by later and later components in the stimulus processing sequence as a task became progressively more difficult. Secondly, sensory discrimination and the genesis of a motor response may arise from neural structures that are activated in parallel with, but are otherwise functionally unrelated to, the event-related response. And thirdly, factors other than difficulty in discrimination may delay the reaction time in some settings. This last hypothesis might explain our observations when the probability of rare tone occurrence was reduced from 14 per cent to 9 per cent in the single trial studies (*see* Table). With this experimental manipulation there was no change in the required sensory discrimination between the two stimuli and there was no change in the event-related potential. There was, however, a reduction in the expectancy of each rare event and the reaction time was significantly delayed. It was as if there were a greater inertia in the motor response system because the target stimulus was less anticipated. A similar uncoupling of the reaction time and sensory discrimination has been reported recently by McCarthy and Donchin (1981). They found that a change in the response compatibility of a task resulted in an increased response latency without concomitant change in the P3 latency, while a change in the stimulus discriminability resulted in an increased latency of both. Which, if any, of these speculations is correct remains for future investigation. The major conclusion to be drawn from our experiments is that the sensory discrimination involved in choice reaction time task can occur much earlier than heretofore appreciated and that the major event-related components of the evoked potential are unrelated in any consistent way either to this discrimination or to the initiation of a motor response, and presumably reflect subsequent events in the neural processing of infrequent target tones.

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NEURAL INPUTS INTO THE NUCLEUS BASALIS OF THE SUBSTANTIA INNOMINATA (Ch4) IN THE RHESUS MONKEY

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SUMMARY

Neurons of the nucleus basalis-substantia innominata-nucleus of the ansa peduncularis complex (Ch4) provide the major source of cholinergic innervation for the entire neocortical surface. In contrast to their widespread projections to all parts of the neocortex, these neurons receive reciprocal projections from only very few cortical areas. Most of the sensory, motor, and association areas in the frontal, parietal, occipital and temporal lobes do not seem to project back to the Ch4 complex. The Ch4 neurons receive their cortical input from prepyriform cortex, orbitofrontal cortex, the anterior insula, the temporal pole, entorhinal cortex and the medial temporal cortex. There are also subcortical inputs from septal nuclei, the nucleus accumbens-ventral pallidum complex and the hypothalamus. This organization suggests that the Ch4 complex is in a position to act as a cholinergic relay for transmitting predominantly limbic and paralimbic information to the neocortical surface. It would also appear that the cortical areas which do not project into Ch4 have no direct way of controlling the cholinergic input which they receive, whereas the limited set of cortical areas which do project into Ch4 can control not only the cholinergic innervation that they receive but also the cholinergic innervation into the entire neocortical mantle.

INTRODUCTION

Extensive pathological alterations have been reported in the nucleus basalis of Meynert in a number of neuropsychiatric conditions ranging from Alzheimer's disease to schizophrenia (Whitehouse *et al.*, 1981; Stevens, 1982). This nucleus is the most conspicuous constituent of a complex region in the basal forebrain which is variably referred to as the subcommissural grey, the sublenticular region, the anterior perforated substance or the substantia innominata. The large and hyperchromic neurons of the nucleus basalis extend from the level of the septum and olfactory tubercle to the level of the lateral geniculate nucleus. These neurons form discontinuous cell islands and intermingle with the fibre bundles of the ansa lenticularis, the ansa peduncularis, the inferior thalamic peduncle, the internal

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capsule, the anterior commissure, the medullary laminae of the globus pallidus and the medial forebrain bundle (Mesulam *et al.*, 1983*a*). Meynert (1872) is credited with the first microscopic description of this nucleus which he named the ganglion of the ansa peduncularis. Since then, several more extensive descriptions of this nucleus have been published (Kölliker, 1896; Foix and Nicolesco, 1925; Papez and Aronson, 1934; Mettler, 1942; Riley, 1943; Gorry, 1963). However, there has been little agreement with respect to the nomenclature for this complex nucleus. Following the designation 'ganglion of the ansa peduncularis' which was introduced by Meynert, terms such as the nucleus basalis, the nucleus of the ansa lenticularis, the nucleus of the septal plane, the preoptic magnocellular nucleus and the substantia innominata have also been used to designate essentially the same assembly of neurons in the primate brain (Papez and Aronson, 1934; Gorry, 1963). It is uncertain whether these terms were intended to designate exactly identical groups of neurons or if, as is far more likely, they referred to overlapping but different portions of the same overall nuclear complex. Perhaps the difficulty in reaching a more uniform nomenclature may be attributed to the organization of the constituent neurons into widely separated islands and to their incomplete demarcation either from adjacent nuclear groups or from the many fibre bundles which traverse the basal forebrain.

Recent advances have considerably reduced the ambiguities inherent in the delineation of the neurons which belong to the nucleus basalis-substantia innominata-ansa peduncularis complex. In the Rhesus monkey, at least 90 per cent of these neurons contain acetylcholinesterase as well as choline acetyltransferase (Mesulam and Van Hoesen, 1976; Poirier *et al.*, 1977; Mesulam *et al.*, 1983*a*). This cytochemical pattern distinguishes the basalis-substantia innominata-ansa peduncularis complex from the adjacent neurons of the globus pallidus, the preoptic region, the lateral hypothalamic area and the amygdaloid complex, none of which contains choline acetyltransferase-positive neurons. A second characteristic of the basalis-substantia innominata-ansa peduncularis complex is its widespread projections to the entire neocortical surface which makes it the major source of the cholinergic innervation in neocortex (Divac, 1975; Kievit and Kuypers, 1975; Mesulam and Van Hoesen, 1976; Mesulam *et al.*, 1983*a*, *b*; Pearson *et al.*, 1983*b*). This pattern of connectivity sets this nuclear complex apart from adjacent cholinergic neurons of the diagonal band nuclei and of the striatum which do not have extensive neocortical projections.

In order to reduce some ambiguities with respect to the nomenclature currently applied to this region, we proposed the designation Ch1 to Ch4 for the four groups of cholinergic projection neurons in the basal forebrain of monkeys and humans (Mesulam *et al.*, 1983*a*). In this nomenclature, the Ch1 to Ch3 groups correspond to the cholinergic neurons located in the medial septum (Ch1) and within the vertical (Ch2) and horizontal (Ch3) limb nuclei of the diagonal band. The designation Ch4 was proposed as a collective term for the entire assembly of choline acetyltransferase-positive neurons which preferentially project to the neocortical mantle and the amygdala. Defined in this manner, the Ch4 group contains neurons which are usually included in the nucleus basalis of Meynert, the substantia innominata, the nucleus of the ansa lenticularis and the nucleus of the ansa peduncularis. The extensive Ch4 complex was further subdivided into anteromedial (Ch4am), anterolateral (Ch4al), intermediodorsal (Ch4id), intermedioventral (Ch4iv) and posterior (Ch4p) sectors, each with a preferential set of neocortical regions as the target for its projections (Mesulam *et al.*, 1983*a*, *b*).

The limited information on the behavioural specializations of the Ch4 complex does suggest that these neurons have response contingencies which go beyond simple sensory processing or motor control. In contrast to the neurons of the globus pallidus which change their rate of firing in temporal relationship to push-pull movements of the limbs and which undoubtedly play an important role in motor control, the adjacent neurons of Ch4 (substantia innominata) in the macaque responded to the delivery of a juice reward (DeLong, 1971). These neurons also responded to the sight and taste of food. The magnitude of this response was influenced by the desirability of the food object and also by the animal's state of hunger (Burton *et al.*, 1975; Rolls *et al.*, 1979). These observations suggest that the Ch4 neurons are especially responsive to motivational states and that they must be receiving an extensive array of sensory and limbic inputs which enables them to associate external sensory events with internal drive states. The pattern of this input influences the type of information processing which occurs in Ch4 and is of considerable importance in unravelling the behavioural specializations of this region.

Neuroanatomical experiments in the macaque have shown the presence of neural projections into Ch4 from the amygdala, the medial frontopolar cortex, the ventromedial hypothalamic nucleus, the magnocellular portion of the dorsomedial nucleus of the thalamus, caudal orbitofrontal cortex and the peripeduncular nucleus (Nauta and Haymaker, 1969; Jones *et al.*, 1976; Leichnetz and Astruc, 1977; Saper *et al.*, 1979; Price and Amaral, 1981). The purpose of this paper is to provide a more extensive analysis of neural inputs into Ch4 and to investigate how the distribution of this input corresponds to the topography of efferent connections from Ch4 to the neocortical mantle.

METHODS

Thirty-seven Rhesus monkey cerebra were available for investigating the neural inputs into the basalis-substantia innominata-ansa peduncularis complex (Ch4). In each animal, an injection of tritiated (^{3}H) amino acids (TAA) was made within cortical or subcortical targets. The injectate consisted of a mixture of ^{3}H-amino acids including proline, lysine and leucine. In each case, the injected volume ranged from 0.1 to 0.4 μl and contained 10 to 50 μCi of radioactivity. For cortical targets, the desired area was exposed directly through a craniotomy. Subcortical targets were reached stereotaxically. All injections were made through a microsyringe attached to a stereotaxic microdrive. Following a survival period of five to ten days, the animal was deeply anaesthetized and perfused transcardially first with saline and then with aldehydes. This range of survival times yields optimal visualization of efferent projections in the Rhesus monkey. The brain was then removed, embedded in paraffin and processed for autoradiography according to the recommendations of Cowan *et al.* (1972).

In essence, the tissue sections were coated with a photosensitive emulsion (Kodak NTB-2), exposed in total darkness at −80° C for 18 to 145 weeks, developed in Kodak D-19 and then fixed and counterstained lightly with thionin. The beta radiation from the TAA causes a precipitation of the silver in the emulsion. Regions that contain the TAA can therefore be identified by the presence of dense silver grains. These grains will be referred to as 'label' in the following text.

The autoradiographic tracing of neural connections with TAA injections has introduced marked improvements in investigating the efferent projections of neurons. The injected TAA are taken up into the perikarya at the injection site, incorporated into newly synthesized protein and transported anterogradely into the axons and terminals in the rapid phase of active transport. Following an appropriate survival time and with the help of the autoradiographic procedures described above, the axons and terminal projection fields of the perikarya within the injection site can be detected by the presence of the silver grain label. The axons that are passing through the injection site do not contribute to the final pattern of labelling since they are not capable of synthesizing new protein even if the injected TAA did find access into the axoplasm. The final pattern of labelling therefore provides a relatively selective map of the efferent projections only of the perikarya situated within the injection site.

In our experiments, the TAA injection site was defined as the region which contained uniformly dense precipitates of label over the neuropil as well as over the perikarya. In each case, all sections through the Ch4 region were examined microscopically with dark-field illumination in order to detect the labelling due to the anterogradely transported TAA. The presence of nonlinear and relatively homogeneous clusters of label within Ch4 was interpreted to indicate labelling within the terminal axonal fields. Cases which contained this pattern of labelling were considered positive with respect to a projection from the injection site to Ch4. Only labelling which was markedly more intense than the background level was taken into consideration. Ch4 labelling predominantly arranged in linear streaks was attributed to passing fibres and not considered to represent a projection from the injection site. When a case was free of label in Ch4, we determined whether it contained the expected anterograde labelling in the striatum or the claustrum before concluding that the neurons in the injection site of that case did not project to Ch4. This allowed us to ascertain that the negative results could not be attributed to the lack of uptake and transport from the injection site, to insufficient exposure time or to technical difficulties in development, fixation and counterstaining.

RESULTS

The anterior part of Ch4 is located just behind the level of the olfactory tubercle, at a point where the anterior commissure crosses from one hemisphere to the other. This anterior sector can be subdivided into a lateral (Ch4al) segment which abuts on the anterior amygdaloid area and a medial (Ch4am) segment which is adjacent to the vertical limb nucleus of the diagonal band (fig. 1). Further caudally, at the level where the anterior commissure loses its continuity, the intermediate sector of Ch4 (Ch4i) can be identified. The ansa peduncularis separates Ch4i into dorsal (Ch4id) and ventral (Ch4iv) subdivisions. Behind the ansa peduncularis, there is the posterior sector of Ch4 (Ch4p) which is surrounded by the globus pallidus, optic tract and putamen (fig. 1). At each level, Ch4 also has interstitial neurons which surround or even penetrate the fibre bundles of the internal capsule, the anterior commissure, the inferior thalamic peduncle and the medullary laminae of the globus pallidus. The identity of these neurons as members of the Ch4 complex is easily determined by their positivity for choline acetyltransferase and their connections with neocortex (Mesulam *et al.*, 1983*a*).

Frontal Lobe TAA Injections

In 9 of the animals (Cases 1 to 9), the TAA injection was made within parts of the frontal lobe (fig. 2). In Cases 1 to 5 the injection site was located within portions of dorsolateral frontal cortex in areas 8, 10, 45 and 46 of Walker (1940) and area 6 of Brodmann (1905). These cases did not contain terminal field labelling in the basalis-substantia innominata-ansa peduncularis complex (Ch4). Cases 6 to 9 were positive in a pattern which was consistent with terminal field labelling within Ch4. In Cases 6 and 7 where the injection site was centred in the lateral part of the orbitofrontal area 12 of Walker, the Ch4 labelling was especially intense in Ch4i (Table). The injection site in Cases 8 and 9 was within the caudal orbitofrontal area 13 of Walker. In these cases, Ch4 labelling was particularly intense in Ch4al and Ch4i (fig. 4). The injection site extended slightly into the claustrum in Case 9 but not in Case 8.

Parietal and Occipital Lobe TAA Injections

In Cases 10 to 14, the injection sites were located within the postcentral gyrus (area 2), the superior parietal lobule (area 5), the inferior parietal lobule (area 7), the medial posterior parietal cortex and the peristriate cortex (fig. 2). None of these cases contained Ch4 labelling above the background level.

Temporal Lobe TAA Injections

Injections that were confined to portions of the auditory association cortex (area TA of Bonin and Bailey (1947) or 22 of Brodmann), in the middle and caudal parts of the superior temporal gyrus (Cases 15 and 16) and those in the visual association cortex (area TE of Bonin and Bailey or 21 of Brodmann) of the middle temporal gyrus (Case 17), did not yield terminal field labelling in Ch4. In Cases 18 and 19 the injection sites were located within portions of the posterior parahippocampal gyrus (area TF-TH of Bonin and Bailey). Of these 2 animals, Case 18 was considered negative because the great majority of Ch4 labelling was in the form of linear streaks and therefore within passing fibres rather than in terminal fields (fig. 5). Case 19 may have contained nonlinear Ch4 labelling slightly above the background level but this could not be established with confidence. In Case 22 which had a TAA injection within the hippocampal formation, terminal labelling was intense in the septal and diagonal band areas but not in Ch4 (fig. 3 and Table).

Cases 20, 21 and 23 to 25 each had substantial Ch4 labelling in a pattern which was consistent with terminal field labelling. The injection site in Case 20 was centred within the medial portion of the inferotemporal visual association cortex (area TEm of Turner *et al.* (1980)) with a minor extension into the perirhinal cortex of Van Hoesen and Pandya (1975). In Case 21, the injection site was confined to entorhinal cortex. In both these animals (Cases 20 and 21), substantial labelling occurred in Ch4al and Ch4i, with a relative peak in the latter subdivision (Table and fig. 6).

[*Text continues on p. 265.*]

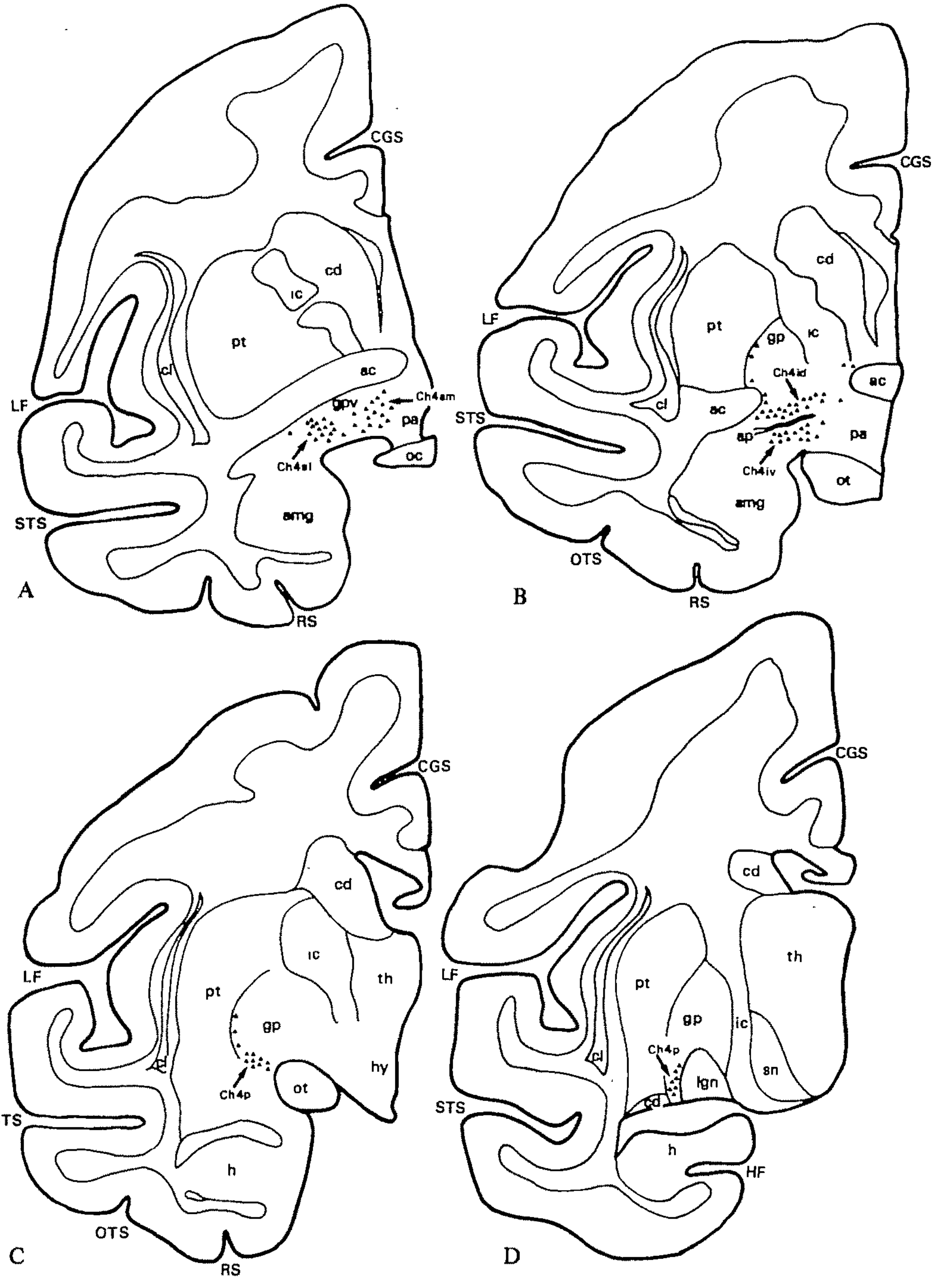

FIG. 1. Location of Ch4 sectors in the Rhesus monkey. Diagrams A–D illustrate sections at progressively more caudal levels of the brain.

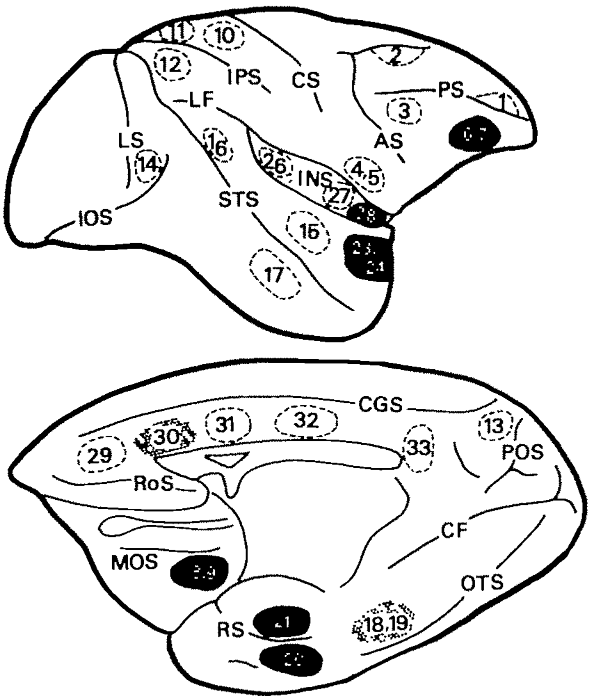

FIG. 2. Representation of the TAA injection sites. The numbers correspond to the case numbers in the Table and in the text. Injection sites surrounded by broken lines indicate cases without Ch4 labelling. Injection sites marked by the black areas indicate cases with positive Ch4 labelling. Cases with questionable Ch4 labelling are indicated by light stippling. *Upper*, lateral aspect of the hemisphere. *Lower*, medial and basal aspects of the hemisphere.

List of abbreviations

ac	anterior commissure
amg	amygdala
ap	ansa peduncularis
AS	arcuate sulcus
cd	caudate
CF	calcarine fissure
CGS	cingulate sulcus
Ch4al	anterolateral division of cholinergic cell group 4
Ch4am	anteromedial division of cholinergic cell group 4
Ch4id	intermediodorsal division of cholinergic cell group 4
Ch4iv	intermedioventral division of cholinergic cell group 4
Ch4p	posterior division of cholinergic cell group 4
cl	claustrum
cs	central sulcus
gp	globus pallidus
gpv	ventral globus pallidus
h	hippocampus
HF	hippocampal fissure
hy	hypothalamus
ic	internal capsule
INS	insula
ios	inferior occipital sulcus
IPS	inferior parietal sulcus
LF	lateral fissure
lgn	lateral geniculate nucleus
LS	lunate sulcus
LSA	lateral septal area
MHY	medial hypothalamus
MOS	medial orbital sulcus
MS	medial septal area
NA	nucleus accumbens
NVL	nucleus of the vertical limb of the diagonal band
oc	optic chiasma
ot	optic tract
OTS	occipitotemporal sulcus
pa	preoptic area
POS	parieto-occipital sulcus
PS	principal sulcus
pt	putamen
PYR	prepyriform cortex
ROS	rostral sulcus
RS	rhinal sulcus
sn	substantia nigra
sts	superior temporal sulcus
th	thalamus
V	ventricle

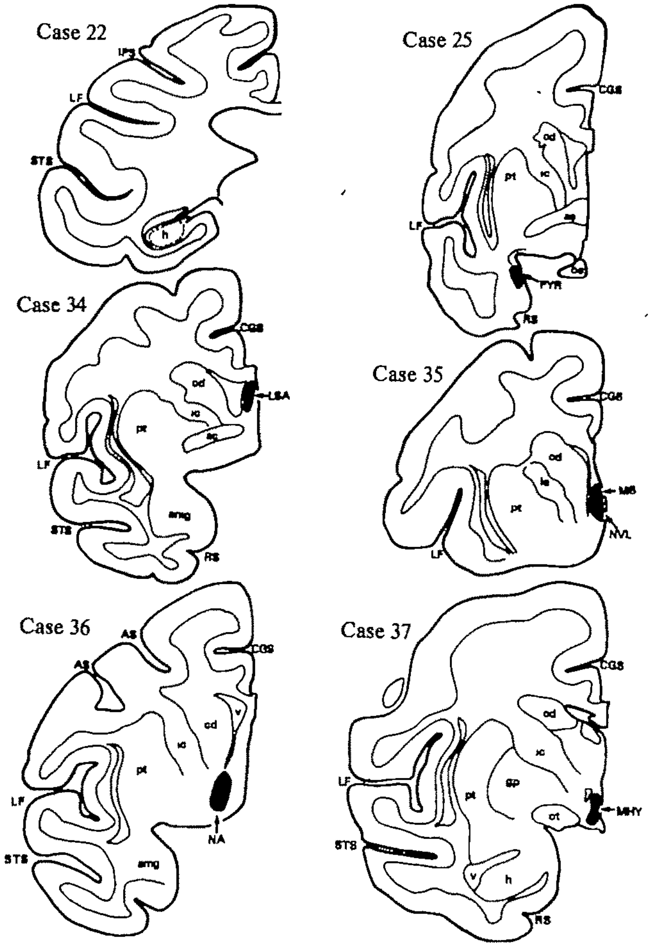

FIG. 3. Representation of the TAA injection sites. Case numbers are the same as those in the Table and in the text. The injection site surrounded by broken lines in Case 22 indicates that this case did not have Ch4 labelling. The injection sites marked in black indicate that these cases contained Ch4 labelling.

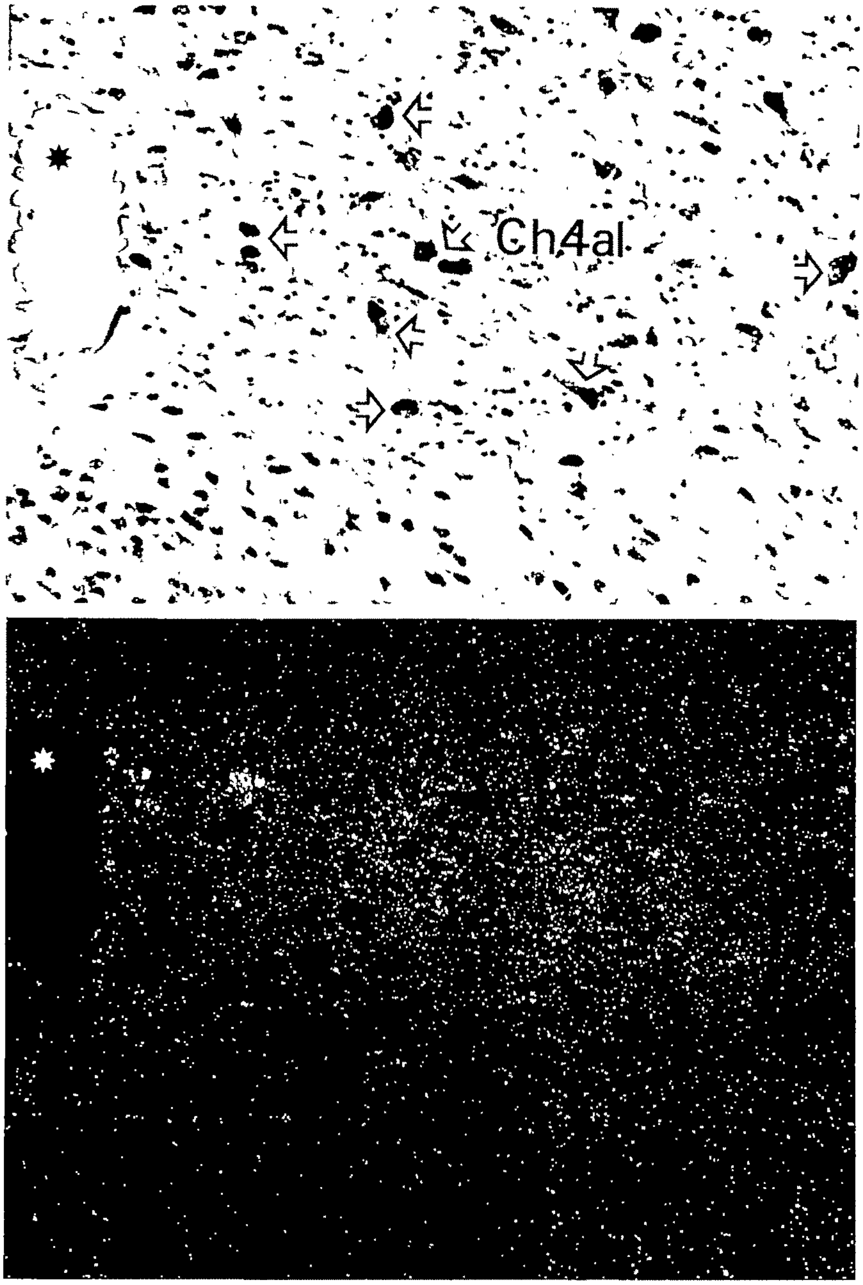

FIG. 4. Photomicrographs from Case 9 which had a caudal orbitofrontal TAA injection site. The upper photomicrograph was taken with bright-field illumination. It shows the part of Ch4al which overlies the most caudal portion of the olfactory tubercle. Open arrowheads point to some examples of the large hyperchromic Ch4 neurons. The smaller neurons at the bottom belong to the olfactory tubercle. The lower photomicrograph shows the same area but under dark-field illumination. This makes the silver label stand out as white dots. The label is clearly concentrated in Ch4al and forms dense homogeneous clusters. Since there are no linear streaks of silver grains, this label represents axonal terminals rather than passing fibres. For purposes of orientation the arteriole in both photomicrographs has been marked with an asterisk. × 266.

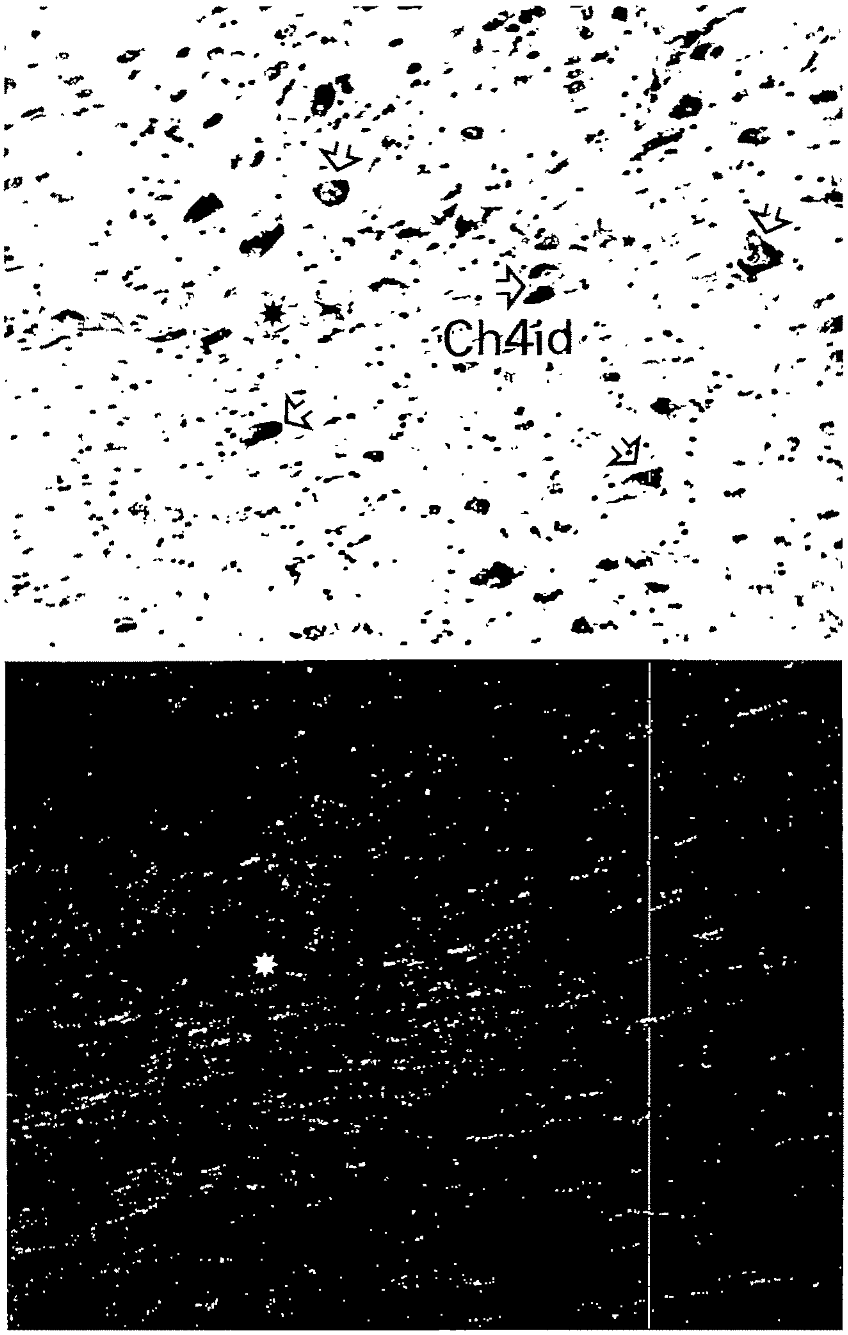

FIG. 5. Photomicrographs from Ch4id of Case 18 which had a TAA injection site in the midcaudal parahippocampal gyrus. The upper photomicrograph was taken with bright-field illumination. Open arrowheads point to some examples of Ch4 neurons. The lower photomicrograph shows the same area but under dark-field illumination. This makes the silver label stand out as white dots. The great majority of the label forms linear streaks and is undoubtedly within passing fibres. This was the only type of label seen in the Ch4 of this case which was therefore considered negative. In the vast majority of the other negative cases even this linear labelling was absent from Ch4. For purposes of orientation the arteriole in both photomicrographs has been marked with an asterisk. ×266.

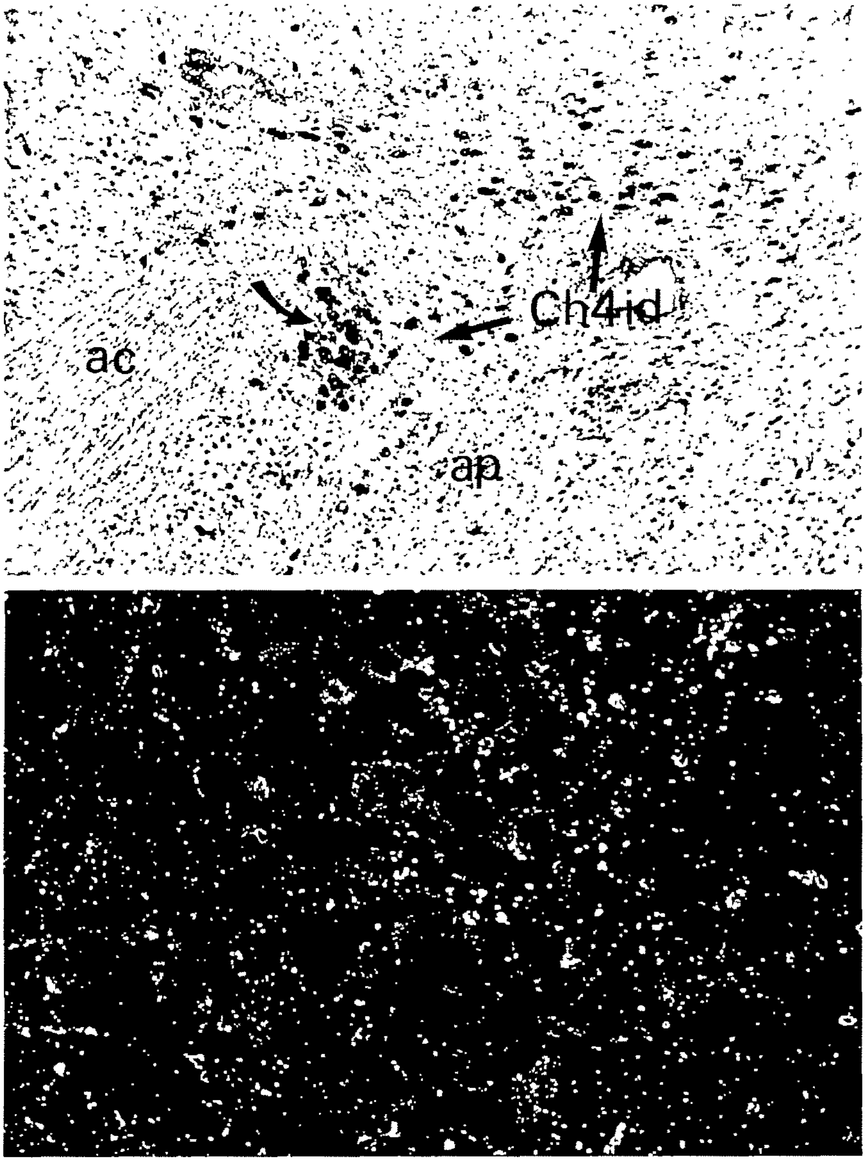

FIG. 6. Photomicrographs from Case 21 which had an entorhinal TAA injection site. *Upper*, bright-field illumination shows two islands of Ch4id (straight arrows). The curved arrow points to the neurons that have been magnified in the lower photomicrograph. × 70. *Lower*, dark-field illumination shows the silver grain label as white dots. This label surrounds the Ch4id perikarya indicated by the curved arrow in the upper photomicrograph. × 500.

TABLE. DISTRIBUTION OF ANTEROGRADE LABELLING WITHIN SECTORS OF Ch4

Case No.	*TAA injection site*	*Distribution of anterograde labelling*				
		Ch4am	*Ch4al*	*Ch4id*	*Ch4iv*	*Ch4p*
1.	Dorsolateral prefrontal (areas 46 and 10)	–	–	–	–	–
2.	Dorsolateral prefrontal (area 8)	–	–	–	–	–
3.	Dorsolateral prefrontal (areas 45–46)	–	–	–	–	–
4.	Frontal operculum (area 6)	–	–	–	–	–
5.	Frontal operculum (area 6)	–	–	–	–	–
6.	Prefrontal-orbitofrontal (area 12)	–	+	+++	+	–
7.	Prefrontal-orbitofrontal (area 12)	+	+	+	++	–
8.	Orbitofrontal (area 13)	+	++++	++++	++++	–
9.	Orbitofrontal (area 13)	–	+++	+	+++	–
10.	Somatosensory (area 2)	–	–	–	–	–
11.	Somatosensory association (area 5)	–	–	–	–	–
12.	Inferior parietal lobule (area 7)	–	–	–	–	–
13.	Medial parietal (areas 5–7)	–	–	–	–	–
14.	Peristriate (areas 18–19)	–	–	–	–	–
15.	Auditory association (area 22 or TA)	–	–	–	–	–
16.	Auditory association (area 22 or TA)	–	–	–	–	–
17.	Visual association (area TE)	–	–	–	–	–
18.	Parahippocampal gyrus (area TF–TH)	–	–	–	–	–
19.	Parahippocampal gyrus (area TF)	–	?+	?+	?+	–
20.	Medial visual association (area TEm + perirhinal cortex)	–	++	+++	+++	–
21.	Entorhinal area	–	++	+++	++	–
22.	Hippocampus	–	–	–	–	–
23.	Temporopolar and superior temporal (areas TG–TA)	–	–	+	+	++++
24.	Temporopolar and superior temporal (areas TG–TA)	–	+	+++	+++	++++
25.	Prepyriform olfactory cortex and endopiriform nucleus	+	++	+++	+++	–
26.	Posterior insula	–	–	–	–	–
27.	Middle insula	–	–	–	–	–
28.	Anterior insula	–	++	+++	+++	+
29.	Anterior cingulate (area 25)	–	–	–	–	–
30.	Anterior cingulate (area 24)	?+	?+	?+	?+	–
31.	Middle cingulate (areas 24–23)	–	–	–	–	–
32.	Posterior cingulate (area 23)	–	–	–	–	–
33.	Retrosplenial area	–	–	–	–	–
34.	Lateral septum	++++	++++	++++	++++	+
35.	Medial septum	+++	+++	+++	++	–
36.	Nucleus accumbens-ventral pallidum	++++	++++	++++	++++	++++
37.	Medial hypothalamus	++	++	+++	+++	+++

The location of the TAA injection site in each case is shown in figs. 2 and 3. In describing the injection site, we used the nomenclature of Walker (1940) for areas 10, 12, 13, 23–25, 45, 46, the nomenclature of Brodmann (1905) for areas 2, 5–7, 18, 19, 22, the nomenclature of Bonin and Bailey (1947) for areas TE, TF, TH, TA, TG and the nomenclature of Turner *et al.* (1980) for area TEM. The negative (–) sign indicates that the terminal field labelling was not above the background level. The plus (+) signs indicate that this type of labelling was above background, + + + + showing the highest level of labelling. The question marks indicate that the presence of labelling could not be established with certainty.

The injection site in Cases 23 and 24 was located within the most anterior and temporopolar part of the superior temporal gyrus, at the junction between areas TA and TG of Bonin and Bailey (fig. 2). Both cases contained intense Ch4 labelling, mostly within the Ch4p sector (Table). In Case 25, the TAA injection site was mostly within the temporal limb of prepyriform olfactory cortex with a minor extension into the underlying endopyriform nucleus (fig. 3). This case contained intense Ch4 labelling, especially in Ch4i.

Insular TAA Injections

In Cases 26 to 28, the injection sites were located within insular cortex, with minor extension into the underlying claustrum (fig. 2). Cases 26 and 27, in which the injection sites were confined to the posterior and middle insula, did not contain terminal labelling in Ch4. Case 28 with a TAA injection in the anterior insula, contained Ch4 labelling in a terminal field pattern, especially in the Ch4i sector (Table).

Cingulate TAA Injections

In Cases 29 to 33, the injection site was located within the cingulate and retrosplenial areas (fig. 2). With the possible exception of Case 30 in the anterior cingulate cortex, none of these cases contained Ch4 labelling within terminal fields.

Subcortical TAA Injections

In Case 34, the injection site was centred within the lateral septal area and in Case 35 within the medial septum and adjacent vertical diagonal band nucleus (fig. 3). Both these cases had intense terminal field labelling within Ch4 which extended to most sectors except Ch4p (Table). In Case 36, the injection site was mostly within the medial portion of the nucleus accumbens but probably also extended into the adjacent ventral pallidum (fig. 3). This case contained intense terminal labelling in virtually all Ch4 sectors (Table). The injection in Case 36 was confined to the medial hypothalamic region and also yielded widespread Ch4 labelling in a terminal field pattern (Table).

The Interpretation of Anterograde Labelling

Two limitations of the autoradiographic method are pertinent to this study. First, very low levels of anterograde transport are extremely difficult to differentiate from background grain. We cannot therefore entirely rule out the possibility that some of the cases which we classified as negative could have contained sparse labelling within Ch4. We used relatively long autoradiographic exposure times in order to decrease the likelihood of such false negative outcomes. Secondly, light microscopic autoradiography often raises the question of whether the label is within terminal fields where synaptic contact occurs or merely in axons on their way to other regions of the brain. This consideration is particularly germane to this study since one property of the Ch4 complex is its intimate association with the many fibre tracks which traverse the basal forebrain. These fibre bundles include the medial forebrain bundle, the ansa peduncularis, the inferior thalamic peduncle, the ansa lenticularis, the medullary laminae of the globus pallidus, the anterior commissure and the internal capsule (Mesulam *et al.*, 1983*a*). In each of the positive cases, one or more of these pathways contained labelled fibres on their way to the striatum, the thalamus, the amygdala, the brainstem and the opposite hemisphere. However, many of the negative cases also contained label in these pathways. Labelled fibres usually yield a distinctive linear streak of silver grain, especially when they run parallel to the plane of section, whereas labelled terminal zones have a more homogeneous distribution of label, especially around perikarya. In all our positive cases, this latter type of distribution was present. However, the possibility that even some of this labelling could be attributed to passing fibres rather than to terminals cannot be ruled out entirely. A complementary way of determining afferent projections is to administer retrogradely transported tracers into the region of interest. This is not practical, however, in this case since Ch4 is embedded within many fibre bundles and since currently available retrograde tracers are readily taken up and transported by passing fibres. A more definitive resolution of this matter will therefore require additional electrophysiological and ultrastructural investigations.

Course of Labelled Fibres

The labelled fibres from orbitofrontal regions (Cases 6 to 9) and from the anterior insula (Case 28) coursed in the external and extreme capsules before entering the region containing Ch4. Fibres from medial (Cases 20, 21) and polar (Cases 23, 24) temporal cortex travelled in a position lateral to the amygdala within the uncinate fasciculus and then curved medially towards the Ch4 complex. The septal projections to Ch4 (Cases 34, 35) coursed mostly within the diagonal band of Broca. The labelled axons from the accumbens-ventral pallidum (Case 36), from the prepyriform cortex (Case 25) and from the hypothalamus (Case 37) were widely distributed within the basal forebrain.

DISCUSSION

The Ch4 complex (nucleus basalis-substantis innominata-nucleus of the ansa peduncularis) occupies a pivotal position in the transmitter circuitry of the brain since it provides the great majority of the cholinergic innervation for the entire neocortical mantle (Mesulam *et al.*, 1983*a*). A large number of complex cognitive and affective behaviours, ranging from memory to aggression, are markedly influenced by pharmacological agents which alter central cholinergic transmission (Drachman and Leavitt, 1974; Butcher and Woolfe, 1982). It is therefore quite likely that the Ch4 complex participates in the modulation of these behaviours.

Pathological alterations in the Ch4 complex have been reported in several neuropsychiatric disease entities. In Huntington's disease and also in schizophrenia, neurons in various stages of degeneration, a decrease of neuronal volume and fibrillary gliosis have been noted in the Ch4 region even though consensus on the universality of these changes is still awaited (Buttlar-Brentano, 1952; Averback, 1981; Stevens, 1982). The most striking and consistent alterations in Ch4 have been observed in Alzheimer's disease and in Parkinson's disease. Ishii (1966) described extensive neurofibrillary degeneration in the Ch4 region (substantia innominata) of patients with Alzheimer's disease. Pilleri (1966) also described massive neuronal loss in Ch4 (nucleus of Meynert) in a patient with Alzheimer's disease and attributed this to retrograde degeneration secondary to atrophy in temporal cortex. The considerable cell loss in the Ch4 complex (nucleus basalis) in Alzheimer's disease has since been documented with greater certainty (Whitehouse *et al.*, 1981; Tagliavini and Pilleri, 1983). The reported loss of choline acetyltransferase activity in the Ch4 region (substantia innominata) of patients with Alzheimer's disease lends further support to these observations (Rossor *et al.*, 1982). Since Ch4 is the major source of cortical cholinergic innervation, loss of neurons in this complex would be expected to result in a decrease of presynaptic cholinergic markers without necessarily leading to a change in the postsynaptic cholinergic receptor density. This is precisely what has been reported in numerous investigations which have found diminished choline acetyltransferase activity and normal muscarinic receptor densities in cortical tissue obtained from patients suffering from Alzheimer's disease (Bowen *et al.*, 1976; Davies and Maloney, 1976; *see* Bartus *et al.*, 1982, for review). These observations suggest that the cell loss in Ch4 and the depression of cortical cholinergic innervation may be closely related to each other in Alzheimer's disease even though the direction of causality has not yet been determined with certainty. In at least one test of memory function, the level of performance in patients with Alzheimer's disease was found to correlate inversely with the cortical choline acetyltransferase activity (Fuld, 1982). Since the Ch4 complex is the major source of neocortical cholinergic innervation these observations give further credence to the suggestion that changes in the corticopetal projections from the Ch4 complex may account for some of the mental changes in Alzheimer's disease.

The basal forebrain may not be the *only* source of cortical cholinergic innervation. An intrinsic component may be provided by the choline acetyltransferase containing cortical neurons which have recently been identified in the rodent brain (Houser *et al.*, 1983). When compared to the input from Ch4, these provide a distinctly minor component of the cortical cholinergic innervation (Wenk *et al.*, 1980; Johnston *et al.*, 1981). Nevertheless, if such neurons also exist in the primate, their contribution to the overall pattern of cortical cholinergic innervation and to its behavioural correlates will need to be investigated in the normal brain as well as in the pertinent disease conditions.

Lewy (1913) and Foix and Nicolesco (1925) reported the presence of degenerative changes in the Ch4 region (basal nucleus) in patients with Parkinson's disease. Subsequently, marked neuronal loss in the Ch4 complex has been observed in the parkinsonism-dementia complex of Guam (Nakano and Hirano, 1983) and in parkinsonian patients who also show a picture of dementia (Whitehouse *et al.*, 1983). As in the case of Alzheimer's disease, and in keeping with the consequences of cell loss in Ch4, a decrease in presynaptic cholinergic markers has also been reported in patients with Parkinson's disease (Ruberg *et al.*, 1982). Although Alzheimer's disease and Parkinson's disease have vast differences in their clinical symptomatologies and their overall neuropathological pictures, it is conceivable that the involvement of the corticopetal cholinergic pathway provides a common denominator for some of the cognitive alterations that occur in both of these degenerative disorders.

When the widespread projections from Ch4 to the cortex and the amygdala are considered, it is unlikely that any single behaviour will emerge as the only behavioural specialization of the Ch4 complex. Instead, it is far more likely that there are multiple behavioural correlations, each reflecting the specializations of the cortical targets that receive cholinergic fibres from the Ch4 complex. For example, the cholinergic projections from Ch4 to paralimbic cortex and to the amygdala may be related mostly to memory and affective behaviour, whereas the pathway from Ch4 to association cortex may also subserve other cognitive functions ranging from language to complex perceptual skills. Whether these behavioural relationships are based on a nonspecific arousing effect of cholinergic innervation or if more specific mechanisms are also involved remains to be seen. Neuronal loss in Ch4 may thus account for widespread mental alterations and may participate in some of the neuropsychiatric changes in Huntington's disease, schizophrenia, Alzheimer's disease and Parkinson's disease. Of all these potential neuropathological relationships, the one between Ch4 and Alzheimer's disease may turn out to have the most biological significance, since the decrease of cortical choline acetyltransferase is profound in this disease and since memory function, which appears to depend on the integrity of central cholinergic pathways, is almost always impaired and usually becomes one of the most important limitations in the mental state of these patients.

In view of these potential pathophysiological relationships, it becomes quite desirable to have a clearer understanding of the neural connections of the basalis-substantia innominata-ansa peduncularis complex (Ch4). Previous experiments in the monkey brain had shown that the Ch4 complex projects to all parts of the cortical mantle (Divac, 1975; Kievit and Kuypers, 1975; Mesulam and Van Hoesen, 1976; Mesulam *et al.*, 1977, 1983*a*, *b*; Pearson *et al.*, 1983*b*). In order to have a better appreciation for the type of neural information that the Ch4 complex conveys to the neocortex, it is also necessary to understand the neural input that Ch4 receives. Our observations in the experiments described above lead to the rather unexpected conclusion that the great majority of the Ch4 connections with the neocortex are not reciprocal. For example, vast portions of dorsolateral frontal cortex, posterior parietal cortex, peristriate cortex, lateral temporal cortex, posterior insula and cingulate cortex do not seem to send projections to the Ch4 complex even though each one of these areas receives inputs from Ch4. The cortical projections into Ch4 arise from the orbitofrontal regions, the temporal pole, the prepyriform cortex, the entorhinal cortex, the medial inferotemporal cortex and the anterior insula. Additional subcortical projections originate in the medial hypothalamus, the septal nuclei and the region of the nucleus accumbens-ventral pallidum. Although we did not have cases with TAA injections within the amygdala, projections from amygdaloid nuclei to the Ch4 complex have been reported by others (Price and Amaral, 1981). The one common characteristic of nearly all these cortical and subcortical projections to the Ch4 complex is that they originate in limbic and paralimbic portions of the brain. This connectivity pattern has important implications for the feedback regulation of cortical cholinergic transmission. The few cortical areas which do have direct projections into Ch4 can potentially influence not only the level of cholinergic signals that they receive but also the cholinergic innervation to other parts of the cortex. Perhaps this is one reason why many of the regions which project to Ch4 are also of crucial importance to memory function. On the other hand, the vast majority of the cortical surface including most of the sensorimotor areas and high-order association cortices have no direct feedback control over the cholinergic input they receive from Ch4. The physiological implications of this arrangement remains to be elucidated. It is reasonable to expect that retrograde cellular changes in Ch4 would be most conspicuous after lesions that involve those cortical areas that do have reciprocal connections with Ch4 since this would damage not only the axons of Ch4 neurons but also the terminals they receive. This may well be the basis of several earlier reports which detected retrograde degeneration in Ch4 following relatively limited temporal lobe damage but not after comparable damage elsewhere in the cortex (Kodama, 1929; Gorry, 1963; Pilleri, 1966). More recently, retrograde cell degeneration in Ch4 has been reported after frontal and parietal lobe lesions as well, but only in cases which contained very extensive cortical damage (Pearson *et al.*, 1983*a*).

Despite considerable overlap, a certain topographical arrangement can be detected in the connectivity from subsectors of the Ch4 complex into neocortex (Mesulam *et al.*, 1977; 1983*a*, *b*). The anteromedial sector (Ch4am) is the major source of Ch4 projections to cortical areas along the medial wall of the hemispheres, the anterolateral sector (Ch4al) to parietofrontal opercular areas, and the intermediate sector (Ch4i) to a variety of dorsolateral frontoparietal, orbitofrontal, insular, peristriate and inferotemporal areas. The posterior sector (Ch4p) is the major source of projections to superior temporal and adjacent temporopolar cortex. The cortical areas that do have reciprocal projections back into Ch4 appear to respect this topography. For example, the input from the anterior insula, the inferior temporal and the orbitofrontal cortex was most concentrated in Ch4i which is also the major source of reciprocal projections to the same cortical areas. The input from superior temporopolar areas, on the other hand, was concentrated mostly in Ch4p, the same sector which is the major source of the reciprocal Ch4 projection into superior temporal-temporopolar regions.

The limbic and paralimbic cortex can be divided into two large classes. On the one hand, the hippocampal and induseal allocortex provide a focus for the paralimbic cortex of the parahippocampal, cingulate and subcallosal regions. On the other hand, the prepyriform allocortex provides a focus for the paralimbic formations of the orbitofrontal, insular and temporopolar regions (Mesulam and Mufson, 1982*a*). It appears that Ch4 is preferentially under the influence of this second set of limbic-paralimbic areas. The behavioural specializations of the insulo-orbitotemporal component of the paralimbic brain are related to autonomic function, feeding behaviour, olfactogustatory sensation, interspecies affiliative behaviour, motivation and some aspects of learning and memory (Mesulam and Mufson, 1982*a*). It is conceivable that the behavioural relationships of Ch4 will also reflect the same set of specializations. Direct connections have been demonstrated from what appears to be the equivalent of Ch4 in the rabbit to the nucleus of the tractus solitarius (Schwaber *et al.*, 1982). Such a projection would allow the Ch4 complex to have a profound influence on the regulation of autonomic function. The heavy projections from the septal nuclei, from the hypothalamus and from the amygdala, are consistent with these behavioural affiliations and also suggest that the Ch4 neurons may be particularly sensitive to the internal milieu. The ventral pallidum and the nucleus accumbens are thought to constitute a limbic component of the extrapyramidal system (Heimer and Wilson, 1975). It is interesting that these regions also project into Ch4. In awake and behaving macaque monkeys, Ch4 (substantia innominata) neurons responded to the delivery of a juice reward and also to the sight and taste of food in a manner which reflected the food preferences and state of hunger of the individual animal (DeLong, 1971; Burton *et al.*, 1975; Rolls *et al.*, 1979). These observations are also consistent with the suggestion that Ch4 neurons are particularly responsive to motivation states. The Ch4 neurons are therefore in a position to act as a cholinergic relay for influencing the activity of the entire neocortex according to the prevailing motivational state.

The responsivity of Ch4 neurons to the sight and taste of food implies that they must be receiving complex sensory information in several modalites. The projections that we have demonstrated indicate several potential routes for this sensory input. The olfactory information appears to have the most direct access to the Ch4 complex from primary olfactory cortex in the prepyriform region. Gustatory, visceral and perhaps also somaesthetic inputs might be relayed through the projections from the anterior insula into Ch4 (Mesulam and Mufson, 1982*b*). Auditory input could reach Ch4 from the anterior portions of the superior temporal region. The projection from the medial inferotemporal region (TEm) to Ch4 could carry information about the visual environment. Additional sensory information to Ch4 could be relayed by the amygdala. These observations show that the Ch4 complex has potential access to all sensory modalities. Except for the olfactory modality, sensory information from cortex reaches Ch4 only after extensive cortical preprocessing since the Ch4 complex does not appear to receive direct input from primary sensory or parasensory regions of the brain in the visual, auditory and somaesthetic modalities.

Cholinergic transmission in the central nervous system has a very ancient origin and can be identified in the brains of reptiles (Desan *et al.*, 1983; Höhmann *et al.*, 1983). The Ch4 complex, however, does not represent a vestigial structure with respect to phylogenetic development. There is a dramatic increase in the prominence of the Ch4 complex in the course of evolution in a manner which seems to reflect the development of the neocortical mantle (Gorry, 1963; Parent *et al.*, 1979; Mesulam *et al.*, 1983*c*). This nuclear complex is quite rudimentary and only incompletely demarcated from the adjacent globus pallidus in rodents, insectivores and carnivores (Gorry, 1963). In cetacea and in primates—especially in man—the Ch4 complex shows a vast increase in size and in differentiation from adjacent nuclear formations. It is therefore not surprising to find that this nuclear formation may be related to complex behaviour and that it may play a role in the alterations in mental state which emerge in the course of several neuropsychiatric disease conditions.

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THE LOCATION OF SPEECH AND WRITING FUNCTIONS IN THE FRONTAL LANGUAGE AREA

RESULTS OF EXTRAOPERATIVE CORTICAL STIMULATION

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SUMMARY

In three patients stimulation of the frontal speech area resulted in one or more of the following symptoms: speech arrest, writing arrest, or impaired rapid alternating movements of the tongue, fingers or toes. Speech arrest could be altered at individual points either with or without impairment of rapid movements or writing, but writing was not impaired without concomitant difficulties with either speech or rapid finger movements.

Our data suggest that the frontal speech area may function to integrate complex motor functions, some speech related and others not. We also confirm previous conclusions that Exner's writing centre is not separate from Broca's area and that the writing defect in Broca's aphasia can occur without involvement of the motor strip.

INTRODUCTION

In 1881, Exner postulated the existence of an area controlling handwriting at the foot of the left second frontal convolution and therefore immediately above Broca's speech area in the third frontal convolution. Although patients with isolated writing disturbances or with pure word muteness ('aphemia') have been reported rarely, patients with Broca's aphasia, in general, demonstrate both writing and speech disturbances (Adams and Victor, 1977).

For many years direct cortical stimulation has been used for the location of areas pertaining to speech and other functions prior to cortical resections (Penfield and Jasper, 1954). Since structural lesions are only occasionally restricted to a single gyrus, techniques based on stimulation of small areas of the cortex may provide additional insights regarding functional localization. We (Lesser *et al.*, 1981, 1982; Leuders *et al.*, 1982) have been using chronic subdural electrodes both for the

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recording of seizures and for the extraoperative localization of speech and other cortical functions prior to surgical excisions. This method obviates the need for patients to remain awake during their craniotomies. In addition, the extraoperative setting allows us to delineate the impairment which occurs with greater precision. We report here the anatomical interrelationships of regions pertaining to speech, writing, and other motor functions in the inferior frontal lobe in three such patients.

PATIENTS AND METHODS

This report concerns three right-handed patients. Case 1 was a 30-year-old woman who had complex partial as well as generalized tonic clonic seizures of twenty-six years duration. Case 2 was a 36-year-old man who had generalized tonic clonic seizures of two and a half months duration. Their occurrence led to the discovery of an arteriovenous malformation in the left frontotemporal region fed from the left internal carotid and middle cerebral arteries. Case 3 was a 34-year-old man who had focal motor seizures of two months duration which led to the discovery of a left frontal tumour, which on biopsy proved to be a malignant astrocytoma.

Case 1 had normal speech. *Case 2* had a mild dysnomia of longstanding. Formal speech evaluation revealed auditory comprehension to be unimpaired, including during conversation and when the patient was given complex information. Reading comprehension was unimpaired, although he felt his reading was somewhat slower than it had been in the past. Verbal output during spontaneous speech and reading out loud was fluent and without dysnomia. Tests of verbal expression revealed occasional difficulties in confrontation naming, although when given the initial sound the patient was able to complete the word with greater than 90 per cent accuracy. On word fluency testing (in which the patient is asked to provide a list of words within a category) the patient provided a somewhat limited list with delays between words and with lists becoming shorter and shorter with each progressive category. When the patient was asked to explain the contents of a picture or explain a proverb, connected speech was normal without any evidence of dysnomia. Tests of graphic expression revealed that the patient wrote a description of a picture which was grammatically accurate, semantically appropriate and without error in punctuation. When asked to write a sentence to dictation, he made some errors of specific elements and when asked to correct his error he continued to display the same mistake. There was no evidence of oral or limb apraxia and rapid alternating movements were performed without difficulty.

Case 3 had a mild dysnomia with intermittent hesitancy of his spontaneous speech. Speech testing of Case 3 showed that the patient was able to comprehend complex ideational information presented at the sentence as well as paragraph level. However, he had difficulty following two-step directions of increasing linguistic difficulty with responses characterized by delays, frequent requests for repetition, and confusion of elements. He was able to read complex paragraphs without error, but the reading rate was slow and he reread paragraphs two or three times to achieve accurate comprehension. Evaluation of verbal expression revealed spontaneous speech characterized by frequent hesitancies, literal paraphasic errors, repetitions and prolongations of initial sounds, and occasional verbal paraphasic errors. When asked to recite automatic speech sequences, there were frequest hesitations. Repetitions at the single word level were unimpaired but at the sentence level were characterized by hesitancies, delayed initiations, and occasional literal and paraphasic errors. Confrontation naming was characterized by literal paraphasic errors and by moderate difficulty with naming numbers and letters and with mild difficulty naming objects, actions, geometric squares, or body parts. The patient was frequently able to correct a literal paraphasic error following one or two repetitions of the word and a delay. Oral reading at the sentence level was slow in rate with more frequent literal paraphasic errors. Word fluency tests were characterized by a limited list, frequent delays between words given, and occasional verbal paraphasic errors (i.e., for the letter 'C' the patient responded 'dog, I mean cat'). Tests of graphic expression were characterized by occasional literal paraphasic errors and by a slow rate of writing. A sentence written to dictation was characterized by verbal paraphasic errors but written confrontation naming was unimpaired. There was no evidence of oral or limb apraxia and the patient was able to perform rapid alternating movements without difficulty.

The electrode plates consisted of strips of stainless steel electrodes 3 mm in diameter and with centre to centre interelectrode distances of 1 cm. These electrodes were imbedded in 1.5 mm thickness silastic rubber with the number of electrodes in the strips designed for each patient. For the purpose of clarity, the electrodes were identified by a common terminology which lettered the vertical column alphabetically from anterior to posterior and numbered the horizontal rows consecutively from superior to inferior (fig. 1). The placed electrodes could be used both for functional localization and for the recording of ictal and interictal seizure discharges. This report will concentrate only on their use in functional localization which was required because of the proximity of functional areas to the regions of operative interest.

Stimulation was first performed between pairs of immediately adjacent electrodes in order to determine the overall orientation of the functional cortical areas. Once this overall organization had been determined, 'distant reference' stimulation was performed between electrodes in the area or areas where functional impairment had been found initially and a second electrode in an area where no functional impairment had occurred initially. This allowed us to determine the location of functional cortical areas with greater precision. We examined two types of functional change in response to stimulation. First, we looked for active contraction of a body part or the occurrence of sensory phenomena in response to stimulation of the resting patient (Table 1). Following this we looked for evidence of interference with performance of an ongoing task during the period of stimulation with resumption of functioning after stimulation ended. The test of functional impairment of speech consisted of asking the patient to read; passages were selected because they were easily readable by the patient. In Cases 1 and 3 the readings were from a paperback novel which the patient had brought to the hospital. In Case 2 the readings consisted of selections from a news magazine. During testing the patient was asked to begin reading from the selection. After the patient had read from one to two sentences stimulation (*see below*) would be applied and the patient would be encouraged to continue reading. After the end of stimulation the patient would continue to be encouraged to read. Writing tasks were as follows. Case 1 was asked to write the name of an object depicted on a card. Cases 2 and 3 were asked to write a sentence description of events of their life both in and out of the hospital. For the latter two patients writing would begin prior to stimulation, and the patient would be encouraged to continue writing during and after stimulation. Thus for each stimulation the patient served as his own control.

As noted above, Cases 2 and 3 had defects in language which might cause literal or verbal errors and Case 3 had slowing of spontaneous verbal output. The scoring which forms the basis of this report therefore did not consider literal or verbal substitutions but only quantitative decreases in verbal or written output during stimulation as compared to the period immediately before. For example, during examinations of graphic function Case 3 was asked to write what he had had for breakfast. After successfully writing 'I had scrambled eggs, toast and milk' on several occasions at other electrodes, he wrote 'I had scrambled scorpion, toast and milk' when testing at electrode C8. He recognized the error immediately after stimulation. On another occasion complete arrest of writing occurred when stimulating at this electrode. However, because of the possibilities of confounding factors related to the patient's underlying speech pathology we thought it best not to count the word substitution as a graphic error for purposes of this report and thus counted C8 as demonstrating an abnormality secondary to stimulation on the occasion of writing arrest and scored no error on the occasion of the substitution. It should be noted therefore that in this report we are dealing with alterations in motor output alone as opposed to alterations in receptive or encoding functions. We considered an alteration to occur if the rate of speech or of writing decreased by at least 50 per cent as compared with the immediately preceding baseline. In practice, however, absolute arrest of writing or speech was found with the exception of electrodes F3 and F4 for speech in Case 2 and electrode C7 for writing in Case 3, where a greater than 50 per cent decrease occurred on repeated testing.

At selected electrodes where reading abnormalities were found in Case 1, we also tested word identification. This task consisted of presenting a picture of a familiar object or a short (one or two syllables) word during stimulation and determining whether the patient was able to name the object or read the word during the stimulation. After stimulation the patient would be asked to recall what word or picture had been presented. In addition, the patient was asked to write the name of the picture twice during stimulation at B3. In all cases the word or picture would be presented to the patient after 2 s of stimulation and taken away before the end of stimulation. A sequential task (counting the numbers from 1 to 20 or reciting the alphabet) was tested at selected electrodes in Cases 2 and 3. In Case 3

TABLE 1. RESPONSES TO STIMULATION OF RESTING PATIENT

Case	*Electrode*	*Inside mouth and throat*	*Lips, face*	*Digit 1*	*Digit 2–5*	*Hand*
1	B2	M	M			
	C1		M			
	C2	M				
	D1		M			
2	D4	M				
	E3		M			
	E4	M				
	F1			M	M	
	F2	M				S
	F3		M			
	F4	M				
3	C5	M				
	D5	M	M			
	D6	S	M			
	D7	S				
	E1				M	
	E2				M	M
	E3		MS			
	E4		M			
	E5	S	M			
	F1			M	M	
	F2				MS	
	F3				S	
	G1				MS	M
	G2				S	
	G3			S		
	G4		S			
	G5	S				
	H1					M
	H2			MS		
	H3			S	S	

M = motor response. S = sensory response. Case 3 had auditory hallucinations, detailed in fig. 1.

spontaneous speech (describing the objects in his living room) was also tested and the patient was asked to carry out verbal commands (pointing at objects in the room or objects on his person) at selected electrodes (Table 2). The results of these tests will be discussed below.

Rapid movements of the tongue were tested by asking the patient to extend the tongue and then move it rapidly in a horizontal or vertical direction. Rapid movements of the fingers were assessed by asking the patient to touch the second to fifth digits with the thumb rapidly and sequentially.

TABLE 2. REPLICABILITY OF ALTERATIONS OF COMPLEX MOTOR FUNCTIONS

Case	*Electrode*	*R*	*Seq*	*Sp*	*P*	*Wo*	*C*	*Wr*	*T*	*F*
1	A1	7			2					
	A2	9			4	3				
	A3	11			4	3				
	B3	4			2				2	
	C1	2								
	C2	4			1				2	
	E1	4								
	E2	5			3	2			1	
	F1	5								
	F2	4								
2	D2	3						3		1
	D3	6						2	4	3
	D4	1	1							
	E3	6							4	
	E4	1	2							
	F1	3								2
	F2	2						2		3
	F3	2							2	
	F4		1							
	G2							2		2
	G3							2		2
	G4	3	2							
3	A6	8					1			
	A7	6		2				2		
	B5	4	1	1				1	1	
	B6	4	1						3	
	C5	1						1	3	2
	C6	6	8				1	6	5	4
	C7	2	1	1				5	1	2
	C8	6	4	1				1	3	4
	D5									1
	D6	2						1	4	
	D7	4	3					1	5	

The Table indicates the number of times alterations in functions were produced at each electrode. In addition, rapid pronation/supination of the hand was impaired twice at D3 (Case 2) and twice at D5 (Case 3) and rapid flexion/extension of the toes was impaired three times at C7 (Case 3). In addition, *see text* for discussion of Case 1. R = reading; Seq = sequential counting or recitation of the alphabet; Sp = spontaneous speech; P = picture identification; Wo = reading of single word; C = carrying out of commands; Wr = writing; T = rapid tongue movements; F = rapid finger movements.

Rapid movements of the toes (Case 3) were tested by asking the patient to flex and extend all five toes in unison. An alteration in function was considered to occur if there was at least a 50 per cent decrease in the rate of execution during stimulation as compared with the rate immediately before and immediately after that stimulation.

In fig. 1 'fingers, hand' refer to points where stimulation of the resting patient resulted in movements of or sensation in one or more digits and/or in the palm, 'face, lips' refers to movement or sensation affecting the cheek or lips and 'mouth, throat' refers to points where stimulation affected the buccal mucosa, tongue or pharynx. 'Functional impairment' (fig. 2) and 'impairment of rapid movements' (fig. 3) indicate points where ongoing speech or writing, or rapid alternating movements, were clearly impaired during stimulation. (In Case 1, handwriting was tested only at electrodes A2A3B3B4, and rapid movements of the tongue were tested only at A2A3B3B4C2C3D3D4E1E2; rapid movements of the fingers were not tested.)

Stimulation consisted of 5 to 8 s chains of 50 Hz bipolar square wave pulses of 0.3 ms duration, produced by a Grass S88 stimulator and delivered through a Grass SIU7 Constant Current Stimulus Isolation Unit. Continuing electrical activity was monitored using two, and at times three, 18 or 19 channel Grass Model 8 Electroencephalographs. Stimulation sessions occurred in the Department of Electroencephalography and were recorded on videotape, with both the patient and electroencephalogram recorded. Sessions lasted from ½ to 3¼ h and occurred over a period of several days. Rest periods were taken if the patient tired. The total duration of the stimulation periods in the three cases were 6¾ h, 4¼ h and 13½ h, respectively. After-discharge thresholds had been determined at each electrode before the detailed functional testing was performed. At the electrodes where functional impairment or impairment of rapid movements were found (i.e. the electrodes indicated in fig. 1B, C) the number of stimulations follows (including, but not limited to, testing of speech, writing or rapid movements). In Case 1 from 3 to 29 stimulations per site (average 16.4) were performed, in Case 2 from 3 to 30 stimulations per site (average 14.3) and in Case 3 from 9 to 74 stimulations per site (average 31.6).

During stimulation, we monitored the electrical activity at all electrodes on the plate and, in particular, looked for evidence of the occurrence of after-discharges. At each electrode we attempted to stimulate at the highest current possible without producing after-discharges and where after-discharges occurred, decreased the amperage of stimulation accordingly. We found that the after-discharge threshold varied from electrode to electrode and that one level of stimulation was not appropriate over the entire plate or even over all electrodes in one area of the frontal or temporal lobe. Were a single intensity of stimulation used, we would have produced after-discharges in some electrodes and stimulated at too low a current at others, possibly missing the presence of functional cortical areas (Lesser *et al.*, 1983).

Thus, although previous authors (Penfield and Roberts, 1959; Ojemann and Whitaker, 1978) have suggested that a 50 per cent error rate can be expected when testing for speech function, we found that when alterations occurred they were consistent over repeated examinations, and we did not accept an alteration as being due to stimulation at a site unless this alteration was consistent (Table 2). We feel that the presence of multiple abnormalities at electrodes where impairment was demonstrated with adjacent 'functionally silent' electrodes argues strongly for the reliability of the method used.

RESULTS

The left hand column of fig. 1 indicates the electrodes where muscle contractions occurred in response to stimulation when the patient was at rest. In Cases 2 and 3, hand/finger, face/lips and mouth/throat areas were well defined. In Case 1, the electrode array did not include the hand/finger area. At some electrodes where muscle contractions occurred in the resting patient (fig. 1A) we also demonstrated functional impairment or impairment of rapid movements (fig. 1B, C).

In all three cases, a region was found surrounding the inferior portion of the rolandic area where stimulation produced impairment of ongoing motor acts but produced no changes when the patient was at rest (figs. 1, 2). In varying combinations these patients demonstrated speech arrest, arrest of writing, or arrest of rapid alternating movements.

Speech arrest occurred without alterations of writing or rapid alternating movements at electrodes A2A3 (Case 1), G4 (Case 2), and A6B5B6 (Case 3). This

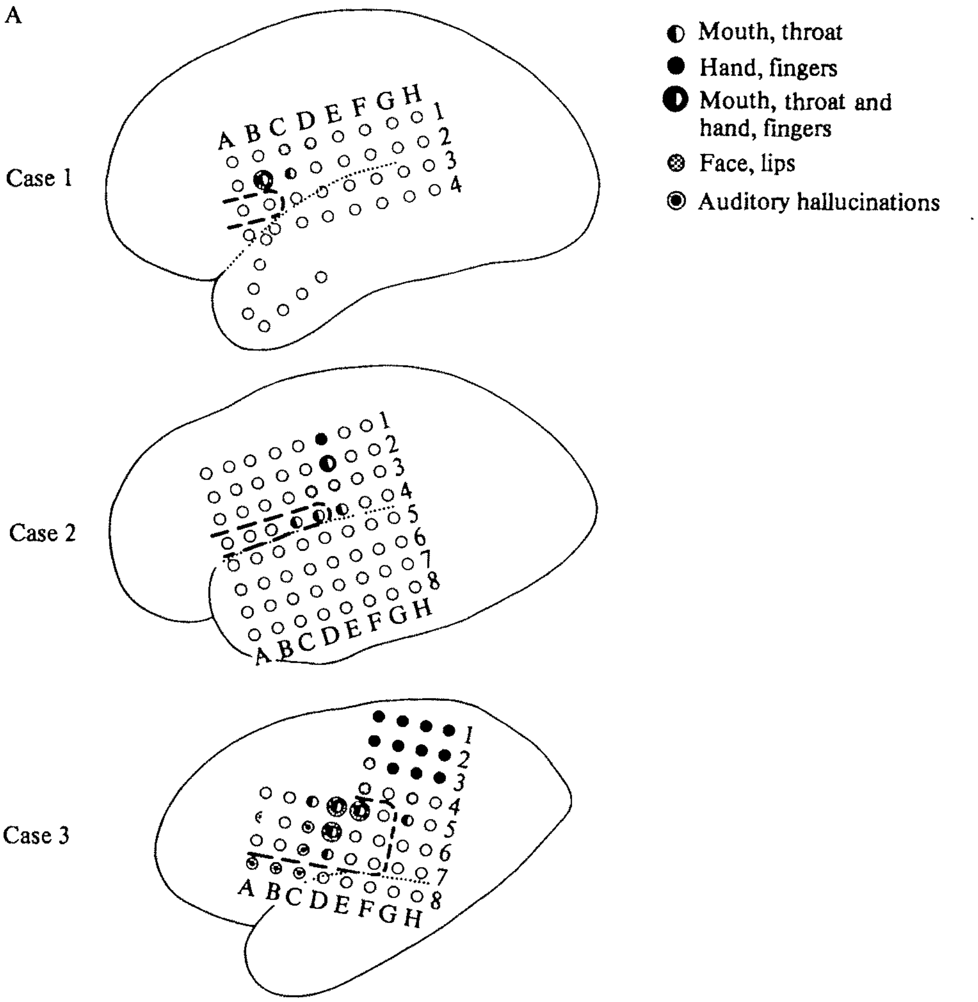

Fig. 1. Results of testing each patient. A (*above*), 'responses', summarizes electrodes where stimulation of the resting patient resulted in motor or sensory changes (i.e. contractions or paresthesiae). The dashed lines indicate the location of the third frontal convolution and the dotted lines the location of the sylvian figure beneath the plate.

[*Fig. 1 continues overleaf.*]

also was found at D4E4F4 (Case 2) but mouth/throat symptoms occurred during stimulation of the resting patient. Speech arrest also was found at A1C1F1F2E1 (Case 1) but writing and rapid movements were not checked at the first four electrodes and writing was not tested at the last one. At C1 (Case 1) there was movement of the lips/face but not the mouth/throat when the patient was at rest.

Speech arrest was associated with altered rapid tongue movements at B3E2C2 (Case 1), E3F3 (Case 2) and D6D7 (Case 3). At D7 (Case 3) both rapid tongue and finger movements were impaired. At rest lips/face but not mouth/throat symptoms

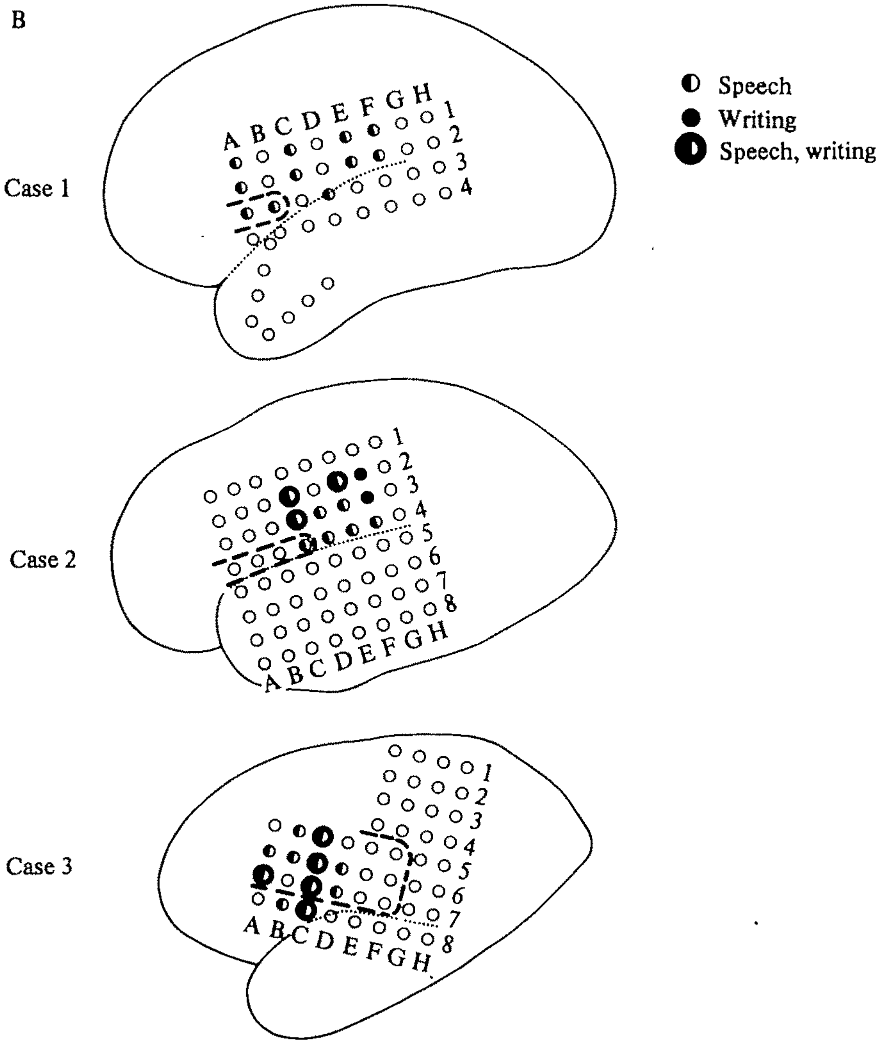

Fig. 1B, 'functional impairment', summarizes points where speech or handwriting was disturbed during stimulation.

occurred at E3F3 (Case 2), mouth/throat but not lips/face symptoms at C2 (Case 1) and D7 (Case 3) and lips/face and mouth/throat at D6 (Case 3). Speech arrest was associated with handwriting arrest at A7 (Case 3) in the absence of altered rapid movements.

Writing arrest occurred in association with alterations of speech, or of speech and both rapid tongue and finger movements. At G2G3 (Case 2) it occurred in association with altered rapid finger movements but with no alterations of rapid tongue movements or speech.

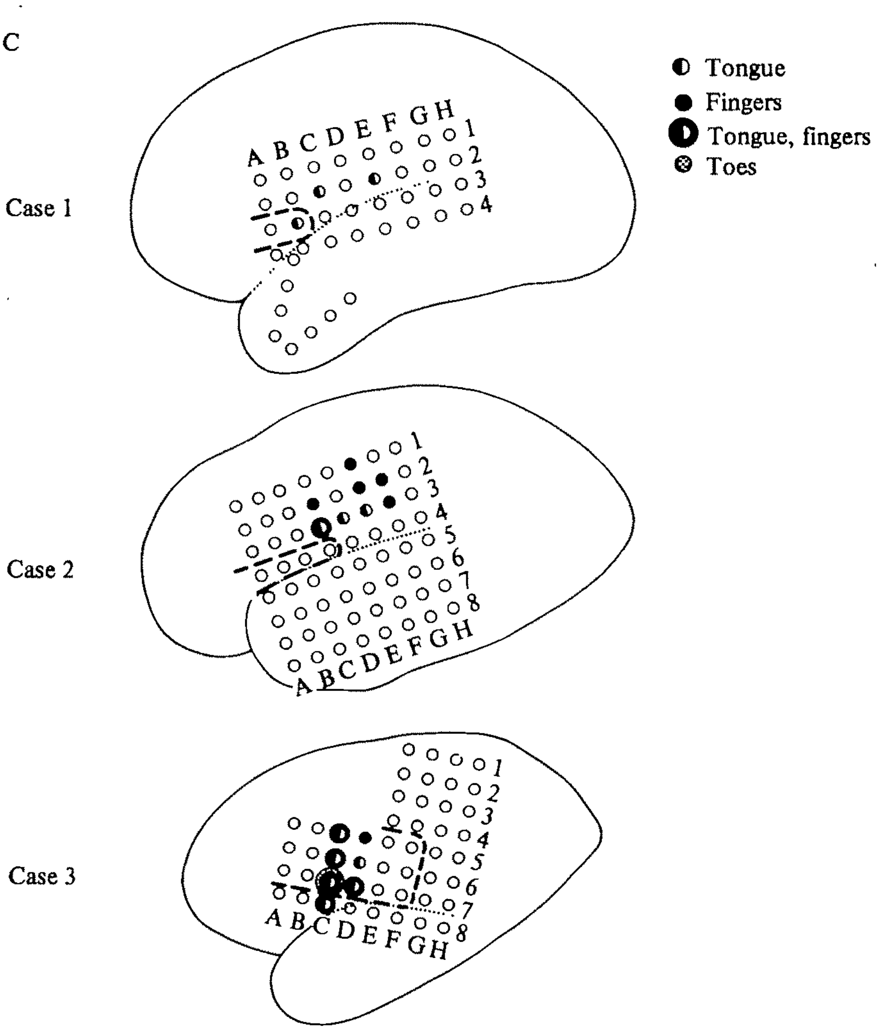

FIG. 1C, 'impairment of rapid movements', indicates where stimulation resulted in the termination of ongoing rapid alternating movements. The dashed lines indicate the location of the third frontal convolution and the dotted lines the location of the sylvian fissure beneath the plate.

In Case 3, rapid foot movements were impaired at C7 and auditory hallucinations were produced at A6A8B8C6–8. The hallucinations were of the patient's own voice saying single words, phrases, or sentences.

Where arrest of speech had occurred during reading it also occurred during counting or reciting the alphabet. In all cases the patient was initially able to perform the sequential task, this would be arrested during stimulation and would resume at the end of stimulation. When Case 3 was asked to carry out commands during

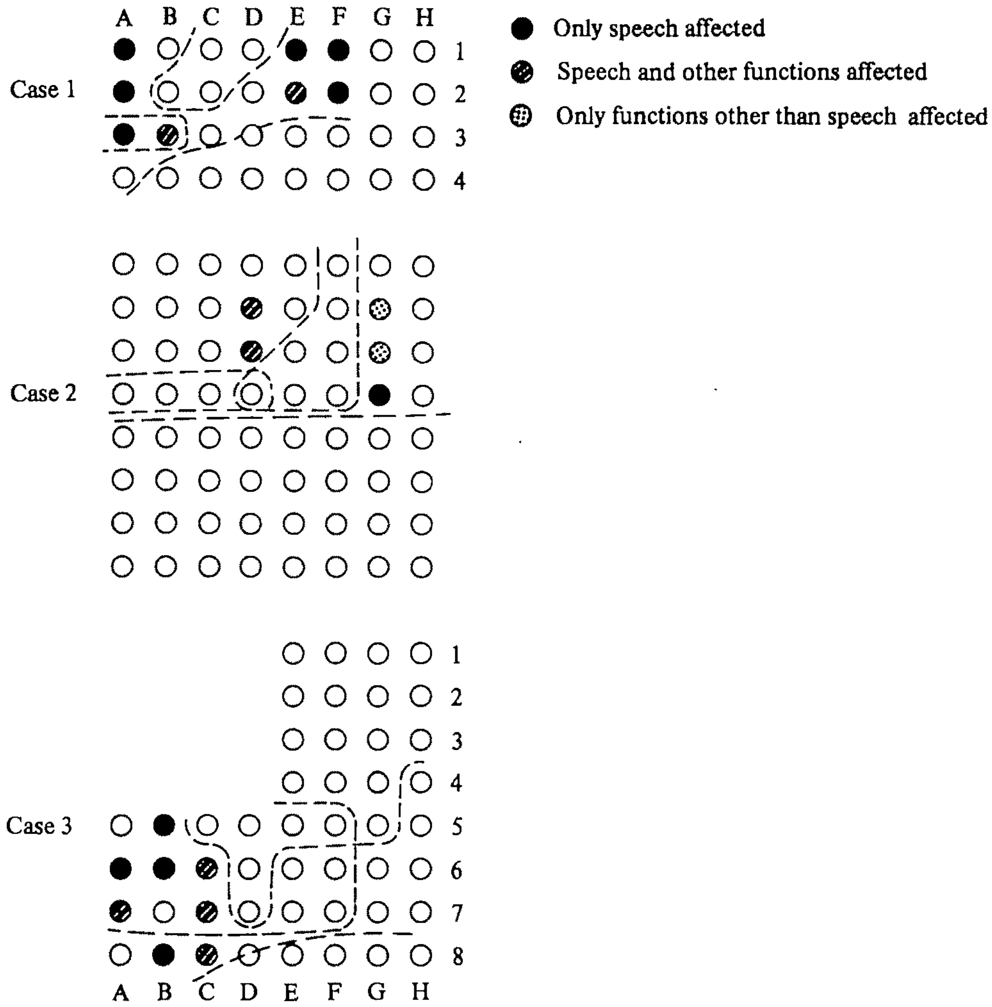
A B C D E F G H
1 2 3 4 5 6 7 8
Case 1
Case 2
Case 3
Only speech affected
Speech and other functions affected
Only functions other than speech affected

FIG. 2. Results of stimulation within the region where impairment of speech, writing, or rapid movements occurred in the absence of muscle contraction in the resting patient. The symbols indicate points where only speech was altered by stimulation, where only functions other than speech were affected, and where speech as well as other functions were altered. Two dashed lines in each illustration indicate the location of the third frontal convolution and of the sylvian fissure, as in fig. 1. The additional line denotes the inferior border of the primary motor strip (*see* 'responses' in fig. 1).

stimulation, we found that he was able to perform these accurately despite the inability to read when tested at other times. At the electrodes where picture identification and single word reading was tested in Case 1, this was always abnormal except at electrode F2 where a picture was named three times during stimulation. At electrode D3 the patient read a single word twice during stimulation and identified a picture twice during stimulation. On two other occasions the patient was unable to identify a picture during stimulation at that electrode, but able to recall what had been presented to her after stimulation was stopped.

Surgical observations indicated that the third frontal convolution included electrodes 3A–B in Case 1, 4A–D in Case 2 and 5A–F, 6A–F and 7A–F in Case 3. The second frontal convolution included 2A–D (Case 1), 3A–D (Case 2) and 3E, 4E (Case 3). In Case 2, the first frontal convolution included 2A–D.

DISCUSSION

Although Benedikt (1865) had stated that graphic functions did not have a specific locus in the neocortex, Exner (1881) postulated the presence of a writing centre at the foot of the second frontal convolution. Subsequent authors have at times agreed with Exner (Mills and Martin, 1912; Nielsen, 1946), denied the presence of a frontal graphics centre (Liepmann and Maas, 1907; Heilbronner, 1910; Russell and Espir, 1961; Leischner, 1969), postulated the presence of a centre located in the temporal-parietal-occipital region (Sérieux, 1891; Wernicke, 1903; Pick, 1903; Nielsen, 1946; Leischner, 1969), described both anterior and posterior graphics centres (Henschen, 1922; Herrmann and Pötzl, 1926; Hécaen *et al.*, 1963), or denied that a purely graphic centre occurs (Wernicke, 1886; Dejerine, 1891; von Monakow, 1914; Pick, 1931; Chédru and Geschwind, 1972). In particular Chédru and Geschwind reviewed the reported cases of pure agraphia and found evidence of dementia, cerebral oedema or an acute confusional state in each patient.

It is often difficult to know the precise location and extent of a cortical lesion at the time a dysfunction such as agraphia is present. Conversely, a lesion, together with its surrounding oedema, which involves Broca's area frequently will also affect the adjacent cortex (Kertesz *et al.*, 1977; Mazzocchi and Vignolo, 1979). Thus it can be hard to separate the effects upon the frontal speech area from those affecting adjacent cortical regions. Lesions of the corpus callosum and of the temporoparietal area can be associated with agraphia, making it unlikely that writing has a single locus in the brain (Leischner, 1969; Hécaen *et al.*, 1963) but the same holds for speech which is accepted to be altered following lesions of Broca's area.

Although two of our patients had structural lesions, speech and writing arrest only occurred when stimulating at specific electrode positions. Moreover, motor responses to stimulation of the resting patient had a distribution (hand/finger superior, face/mouth inferior) appropriate for primary motor cortex. These findings strongly suggest that our observations accurately reflect the functional anatomy of the regions tested. Therefore, it appears that agraphia can occur due to restricted lesions of the frontal lobe. However, although we found areas with isolated speech disturbances, agraphia was always associated with impairment of other complex motor acts.

Broca's area can be defined by the occurrence of speech arrest in the absence of muscle contraction in response to stimulation of the speaking patient. As has been noted previously, it could occupy any of the three convolutions in front of the inferior precentral gyrus (Penfield and Roberts, 1959). Cases 1 and 2 of Ojemann and Whitaker (1978) demonstrated speech arrest in response to stimulation at sites posterior to the motor strip as did two of our patients. These authors commented on the wide variability between patients but concluded that arrest of speech could consistently be produced only by stimulation of a narrow portion of the inferior frontal lobe immediately anterior to the motor strip (Ojemann and Whitaker, 1978; Ojemann, 1979). Our results are in accord with these authors in that speech arrest was produced in all three patients only at points just anterior to the motor strip. We wish to emphasize the fact, however, that, in individual patients, speech arrest could also be produced at other sites.

Although supporting cases had been described earlier (Tuke and Fraser, 1872–1873; Burckhardt, 1890–1891), the concept that 'the third left frontal convolution has no special language function' was advanced most importantly by Pierre Marie (1906) who felt that defects of motor language could be the result of lesions in a broader area within the opercular region as well as within the lenticular nucleus and insula. Penfield and Roberts (1959) agreed that 'Marie was probably correct . . . that Broca's area could be sacrificed without eventual loss of normal speech'. Finally, LeCours and Lhermitte (1976) described a case of pure anarthria due to a frontal lobe lesion sparing Broca's area. All these observations serve to emphasize that the entire opercular region has important functions related to motor speech, rather than this being localized only to the foot of the third frontal convolution (Bruyn and Gathier, 1969; Mohr *et al.*, 1978; Levine and Sweet, 1982) and thus support our finding a more widespread distribution of sites where stimulation resulted in speech arrest.

Rasmussen and Milner (1975) concluded that stimulation of the speech zone produces a disturbance of speech without interference of movements of the lips, tongue, or larynx whereas Ojemann and Mateer (1979) were able to demonstrate alteration in orofacial movements within the human language cortex. In our patients a number of complex motor functions were impaired including speech, writing, and rapid alternating movements and the regions affecting these were not sharply delineated from one another. In agreement with Ojemann and Mateer (1979), we found sites within the language area where stimulation impaired speech as well as rapid movements although, at other sites, only speech arrest could be produced. In agreement with Penfield and Rasmussen (1957) and Woolsey *et al.* (1979) stimulation within the opercular region could affect the hand and foot. These findings serve to emphasize that the 'speech area' controls more than speech and, in fact, as early as 1878 Hughlings Jackson described impaired tongue protrusion in certain aphasics. Subsequently, a number of reports (Foix *et al.*, 1926; Alajouanine and Thurel, 1933; Alajouanine *et al.*, 1959) emphasized the importance of the inferior posterior frontal lobe in controlling facial-lingual-masticatory movements, and more recent authors (De Renzi *et al.*, 1966; Mohr *et al.*, 1978; Levine and Sweet, 1982) have concluded that oral apraxia commonly accompanies Broca's aphasia. All these papers support the finding in our patients of both speech and nonspeech related functions in close approximation within the tested region.

Geschwind (1965) in his discussion of disconnection syndromes commented on the 'probable incorrectness of the classical distinction between aphasic and apraxic agraphia' and quoted the observations of Liepmann (Liepmann and Maas, 1907; Liepmann, 1908) 'that the left hemisphere is dominant for more than speech'. In this paper Geschwind also reviewed the data indicating that the primary intrahemispheric connections in the macaque are to the premotor rather than the motor cortex (Ward *et al.*, 1946; Sugar *et al.*, 1948) and suggested that the facial apraxia seen in Broca's aphasics was most likely due to destruction of the premotor region. Other authors (Woolsey *et al.*, 1952; Kuypers, 1973; Woolsey *et al.*, 1979; Levine and Sweet, 1982) have emphasized the data indicating a more anterior localization for regions mediating axial and proximal limb musculature (i.e. area 6) and more caudal localization for regions mediating more distal musculature (i.e. area 4). In our study, Cases 2 and 3 demonstrated (fig. 1) impaired rapid finger movements at electrodes where responses had also occurred to stimulation at rest, presumably an electrophysiological marker for the primary motor strip. In addition, however, rapid movements were impaired at electrodes anterior and posterior to this region. Although the area anterior to the primary motor strip was relatively narrow, this is consistent with the narrowing of the inferior portion of area 6 on Brodmann's map (Truex and Carpenter, 1964). An alternative explanation would be that the motor inhibition that we found was in response to stimulation of area 4S (Dusser de Barenne and McCulloch, 1939), on the rostral border of area 4. In any event it appears that rapid movements could be impaired at sites stretching from in front of to behind the primary motor strip and therefore that both 'motor' and 'premotor' lesions can result in apraxias.

Geschwind (1965) did not feel that available data was sufficient to demonstrate that a right hand apraxia could be due to a left premotor lesion due to the proximity of the primary motor cortex. De Renzi *et al.* (1966) noted that the correlation between oral apraxia and aphasia was stronger than the correlation between oral and limb apraxia. Finally, Levine and Sweet (1982), although noting that the hand and mouth areas could overlap, nonetheless concluded that writing arrest would be produced by a more superior and speech arrest by a more inferior lesion. The conclusions of these authors, however, were based upon patients with aphasic and apraxic disturbances due to structural lesions. Although all three of our patients had seizures and two had other cortical lesions, none of these factors are likely to account for the self-limited impairment of writing or of sequential finger movements which resulted from stimulation. We therefore can conclude that the inferior posterior frontal region functions as a 'motor association area' (Geschwind, 1965), integrating speech as well as other complex motor acts and with lesions of this region resulting in functional apraxias (Mohr *et al.*, 1978; Levine and Sweet, 1982) including apraxias of writing and of rapid finger movements. Thus 'Exner's writing centre' most probably represents one of the component functions associated with Broca's area.

The intact picture identification at electrode F2 in Case 1, where speech arrest had occurred four times during the reading task, suggests that a continuous performance task such as we used may be a more sensitive indicator of speech arrest in this region. It should be emphasized that during the trials which produced arrest of picture identification or word reading, the patient was able to recall what had been presented after the end of stimulation. This indicates that what we had produced was arrest of the motor act of speech ('aphasic arrest', Penfield and Roberts, 1959) rather than interference with other functions related to language. We did not find difficulties in recall of the presented word or picture as has been described by Fedio and Van Buren (1974) and Ojemann (1978). This might be accounted for by the differences between our naming task and that utilized by these authors.

In Case 3, auditory hallucinations were produced by stimulation within the frontal speech area. This had been found previously only within the temporal lobe (Penfield and Roberts, 1959; Gloor *et al.*, 1982) and Penfield and Perot (1963) concluded that words or experiential responses did not occur during stimulation of the speech area itself. However, analogous to Wernicke's (1886) suggestion that writing represents the copying of the visual image of letters, a close functional relationship could be postulated between the inner experience of language and the production of words. Levine and Sweet (1982) similarly noted that the macaque region analogous to the third frontal convolution in man had numerous connections to auditory and visual association cortex. On the other hand, since we did not record from limbic structures in this patient, we cannot exclude the possibility of spread of the stimulation effect to this region from the neocortex, as has been suggested elsewhere (Gloor *et al.*, 1982).

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SELECTIVE COGNITIVE IMPAIRMENT DURING FOCAL AND GENERALIZED EPILEPTIFORM EEG ACTIVITY

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SUMMARY

It is well established that generalized epileptiform EEG discharges unaccompanied by overt clinical change may nevertheless be associated with transitory cognitive impairment (TCI) detectable by appropriate psychological testing. However, the tests employed in most research studies of this phenomenon are of little use for routine clinical application. They are suitable for administration only over short periods of time and are therefore applicable only to patients with a high discharge rate, a serious limitation, as the discharges are generally depressed by the tests themselves.

We have developed two short-term memory tasks, one using verbal, the other nonverbal material presented in the form of television games which patients are generally prepared to perform for up to an hour or longer. Forty-six patients with subclinical EEG discharges have been studied. They were screened by video monitoring before and during testing to exclude any with overt clinical changes during the discharges. Despite this rigorous selection, in 50 per cent TCI was demonstrable with a confidence level (within the individual patient) of 10 per cent. Discharges during stimulus presentation were most disruptive of performance and those confined to the period when the patient was responding were without demonstrable effect. A significant association was found between the laterality of focal or asymmetrical generalized discharges and impairment of one or other task, left-sided discharges being associated with errors in the verbal task and right-sided with impairment of the nonverbal test.

Two case histories are cited illustrating patients who were clearly handicapped by TCI and whose functioning improved when the subclinical discharges were suppressed by medication. To determine how many patients suffer such disabilities or can be helped by appropriate medication, further prospective studies are required.

INTRODUCTION

Epileptiform EEG discharges occur without evident clinical concomitants in many patients with epilepsy, and also in some persons who are not known to suffer from seizure disorders. The discovery by Berger (1933) of generalized 3 Hz high voltage activity accompanying the absence seizure was rapidly followed by the realization (Gibbs *et al.*, 1936) that this relationship was not invariable and that brief generalized spike-wave bursts could occur without apparent clinical change. This view had in turn to be qualified when Schwab (1939) succeeded in demonstrating that 'subclinical EEG discharges' were often accompanied by an increase in reaction time or indeed by complete failure to respond to a stimulus. Many subsequent studies have reported transitory cognitive impairment during subclinical spike-wave activity. Most, however, gloss over the problem of distinguishing overt absence seizures with global unresponsiveness from EEG discharges accompanied by subtle cognitive changes detectable only by suitable testing. A minority of authors (*see* Shimazono *et al.*, 1953; Kooi and Hovey, 1957; Yeager and Guerrant, 1957; Davidoff and Johnson, 1964; Guey *et al.*, 1965; Porter *et al.*, 1973; Goode *et al.*, 1970) have documented behaviour during the investigation and few have compared performance during subclinical discharges with that during visible absences. This is regrettable as it has been shown (Tizard and Margerison, 1963*a*; Goode *et al.*, 1970) that the probabilities of detecting a cognitive deficit and of observing an absence both increase with duration of the discharge. Very few studies are specifically restricted to patients exhibiting no overt seizures during the investigation (Hutt and Gilbert, 1980) or include patients not considered to suffer from epilepsy (Ishihara and Yoshii, 1967).

The concept of 'subclinical' EEG discharges has been used, sometimes under other names such as 'larval seizures', by many authors (Gibbs *et al.*, 1936; Shimazono *et al.*, 1953; Kooi and Hovey, 1957; Yeager and Guerrant, 1957; Tuvo, 1958; Tizard and Margerison, 1963*a*; Davidoff and Johnson, 1964; Grisell *et al.*, 1964; Hutt and Fairweather, 1973), but itself presents difficulties. Involuntary movements during a seizure will not readily be recognized by an observer unless they differ from the patient's interictal behaviour. Stereotyped ictal movements falling within the subject's normal behavioural repertoire may be detectable only by careful analysis of simultaneous EEG and video recordings. Impairment of normal functions may be even more difficult to recognize: during routine EEG recordings there is little behaviour to be seen. Conversely, during telemetric monitoring a patient may be engaged in activities too unpredictable for the observer to be able to detect a momentary decrement of performance. An EEG discharge can therefore be classified as 'subclinical' only in so far as the available methods of clinical observation, applied under particular circumstances, fail to show any change in the patient. In the present text the term 'transitory cognitive impairment' (TCI) is used to designate functional deficits demonstrable by suitable testing, during spike or spike-wave discharges, which are subclinical in the operational sense indicated above.

Some authors consider that generalized spike-wave activity is always accompanied by impaired performance (Kooi and Hovey, 1957), or that 'interseizure discharges probably do not occur in absence seizures' (Delgado-Escueta, 1979). Others have been unable to demonstrate TCI during such discharges (Milstein and Stevens, 1961; Prechtl *et al.*, 1961). Various authors, notably Tizard and Margerison (1963*a*) and Mirsky and Van Buren (1965), have demonstrated that some tests are more sensitive to the effects of epileptiform activity than others: simple motor tasks such as rhythmic tapping, simple reaction time, or tracking, are relatively little affected by generalized spike-wave activity (Schwab, 1941; Cornil *et al.*, 1951; Shimazono *et al.*, 1953; Yeager and Guerrant, 1957; Tuvo, 1958; Hauser, 1960; Tizard and Margerison, 1963*a*; Davidoff and Johnson, 1964; Grisell *et al.*, 1964; Mirsky and Van Buren, 1965; Chatrian *et al.*, 1970; Goode *et al.*, 1970; Porter *et al.*, 1973; Browne *et al.*, 1974), whereas choice reaction time (Tizard and Margerison, 1963*b*; Sellden, 1971; Hutt *et al.*, 1977), signal detection (Tizard and Margerison, 1963*a*; Mirsky and Van Buren, 1965; Hutt *et al.*, 1976) and short-term memory tasks (Shimazono *et al.*, 1953; Jus and Jus, 1962; Geller and Geller, 1970; Hutt, 1972; Hutt and Gilbert, 1980) are more sensitive.

Although any attempt to equate epileptiform activity with epilepsy is in general to be deplored, the occurrence of a paroxysmal change in cerebral electrical activity simultaneously accompanied by cognitive impairment meets generally accepted definitions of an epileptic seizure (Lennox, 1960). Whether or not the conclusion of Tizard and Margerison (1963*b*) is accepted, that such an event 'should be considered evidence of a seizure', TCI is likely to be of practical importance. Such episodic impairment may be a disability (causing problems of education or at work) or a danger (when the patient is driving, or is exposed to common domestic hazards). There appears therefore to be a clinical indication to test for TCI in patients exhibiting frequent generalized epileptiform discharges without overt seizures. Indeed an evaluation study of a clinical EEG and video monitoring service (Binnie *et al.*, 1981) showed that patients were often referred with the request to determine whether or not known EEG discharges were accompanied by clinical changes. Often the video recordings revealed brief minor seizures which had not previously been observed, but to address the question adequately in patients without visible attacks it seemed necessary to add psychological testing to the monitoring techniques.

Most published studies of TCI concern highly selected patients with frequent epileptiform discharges and the tests used were hardly suitable for clinical purposes. A routine test for TCI should fulfill the following criteria (Binnie, 1980). (1) The task must not so suppress epileptiform activity that testing is impossible. A high level of arousal generally reduces epileptiform activity, moreover intense stimuli may abort the discharges and elicit normal responses (Schwab, 1941; Shimazono *et al.*, 1953; Tizard and Margerison, 1963*b*; Goode *et al.*, 1970). (2) The test must be acceptable for administration over a period sufficiently long for the effect, if any, of an adequate number of discharges to be observed. In practice, patients must generally be willing to perform the task for at least half an hour. (3) The difficulty must be adaptive to the patient's level of performance. Easy tasks are relatively insensitive to TCI (Hutt, 1972; Hutt *et al.*, 1977), but increasing task difficulty may either decrease or increase the amount of epileptiform activity (Tizard and Margerison, 1963*b*; Hutt, 1972). (4) The task must continuously test cognitive activity (Guey *et al.*, 1965; Goode *et al.*, 1970); if it is intermittent, discharges may fall in the intervals between trials. Intermittent testing triggered by the discharges themselves (Binnie and Lloyd, 1973; Porter *et al.*, 1973) is not an acceptable solution. Discharge probability is influenced by the state of awareness, and epileptiform activity may therefore occur preferentially when the patient is inattentive. (5) The test should have face validity. The clinical relevance is more obvious if the cognitive impairment demonstrated is of practical importance, as for instance impaired verbal memory in a school child or increased reaction time in a motorist. (6) To give greater insight into the nature of TCI, the test, or tests, should differentiate between different psychological functions and between different regions of the brain.

The authors have developed several tests intended to meet these criteria but only the two which have proved to be most satisfactory will be described. Both were short-term memory tests presented as television games. The material to be recalled was topographic in one case and verbal in the other.

MATERIAL AND METHODS

Tests

In the topographic task, the patient was presented with 7 randomly coloured rectangles (height 23 mm, width 35 mm) distributed irregularly against a dark green field on a 440 mm colour TV monitor. These flashed off and on in a random sequence, one rectangle at a time being blacked out for 650 ms with a 250 ms interval between extinctions of successive rectangles. The extinction of each rectangle was accompanied by a tone. On completion of the sequence all the rectangles became white. The patient was then required to reproduce the sequence by pointing at the rectangles in turn with a light-pen. Each correct response elicited the tone previously presented with that rectangle. An incorrect response elicited a low frequency tone and flashing of the rectangle which should have been selected, and terminated the current test run. The next trial began 4 s after completion of the correct sequence or after the occurrence of an error. The task was therefore self-paced. The sequence length was adaptive to performance: when two consecutive sequences were correctly reproduced the entire series length was increased by one; two consecutive errors resulted in the sequence being reduced by one. Colour and sound effects were used to make the task entertaining and a correct response caused a simple tune to be played. However, sound and colour did not provide information which could be used to assist recall of the sequence: the sounds and colours associated with each rectangle were randomly changed after every trial and during the response phase the display was colourless. The task, it will be noted, had some similarity to Corsi's blocks test (Milner, 1971) and also to a popular computer toy.

The second, verbal, task used so far as possible a similar form of presentation and response. Words of four letters (height 14 mm, width 9 mm) were displayed consecutively in the centre of a television screen, each for 650 ms separated by intervals of 250 ms. The sequence had then to be reproduced by means of the light-pen from a list of 7 words arranged vertically in the middle of the screen. The words were selected as being simple, emotionally neutral, not readily assembled into sequences based on meaning or alliteration, and containing no repetitions of characters. The following (Dutch) names of animals were used: duif, hond, geit, mier, spin, poes, kalf.

Both tasks were presented by means of a microcomputer, which also annotated the EEG chart with a pulse code indicating stimulus presentation and correct or incorrect responses. The program, written in BASIC with assembler subroutines, currently runs on an Apple II computer, and is available from the authors. A revised version for a Z80 with colour graphics (Kontron Psi 80) is in preparation.

Patients

The patients were all in the first instance referred to the Department of Clinical Neurophysiology, Instituut voor Epilepsiebestrijding, Heemstede, for investigation of epilepsy. Patients were selected for possible testing on the basis of the following criteria. (1) Presence of paroxysmal EEG discharges, either frank epileptiform activity (spikes or spike-wave complexes or sharp waves) or paroxysmal theta or delta bursts, whether generalized or focal, in the eyes open condition, exclusive of findings during hyperventilation, photic stimulation or after sleep deprivation. (2) Absence of overt clinical manifestations accompanying such discharges. The routine practice of the department includes such measures as recording with the patient seated in an upright position, asking the patient to count or press regularly on a button or to repeat simple phrases to determine whether performance is impaired, or muscle tone lost, during subclinical discharges (Binnie *et al.*, 1982). Patients in whom clinical changes were detected by such methods were excluded. (3) Mental and physical capacity considered to be compatible with performance of the tests (children of average intelligence from 8 yrs upwards were generally able to perform both tasks). (4) Agreement of the referring neurologist that a clinical indication existed for determining whether or not the patient's discharges were accompanied by TCI.

Procedure

Prior to testing, preliminary EEG recording of some 30 to 60 min duration was performed by 16- or 20-channel cable telemetry (Kamp *et al.*, 1979) with continuous video monitoring in a sitting room which provided a normal domestic environment (Binnie *et al.*, 1981). During monitoring the patients sat with eyes open, read, talked or played card or board games. If the number of discharges occurring under these conditions was considered inadequate (generally less than 1 per 5 min) patients were excluded from further study, as were any exhibiting overt epileptic seizures during this period.

During testing, the patient was seated in an upright chair in front of the television monitor in a quiet room with subdued lighting. Behaviour was monitored and tape-recorded by closed circuit TV in order to exclude any patients exhibiting overt seizures. As indicated above, it may be considered that the phenomenon of TCI itself calls in question the definition of a seizure. However, the operational criterion employed was the occurrence during an epileptiform EEG discharge of abnormal movements or behaviour, staring or obvious akinesia, eyelid flutter, or subjective changes resembling the patient's habitual ictal phenomena. In practice only 2 patients were excluded on these grounds: one had absence attacks (staring and eyelid flutter), the other displayed massive myoclonus, which strikingly increased in frequency with task difficulty. During the period of the study 1059 patients of more than 8 years of age attended for EEG investigation; 62 were rereferred for evaluation of possible TCI, 53 were considered to meet the criteria for testing and 2 of these were eliminated because of overt seizures during the test. One patient had to be excluded due to a lack of discharge-free trials and 4 others exhibited too little epileptiform activity to permit assessment.

Data Analysis

The test may be considered as a series of trials, each comprising, first, the presentation of the stimulus sequence and then the response. Each record was analysed to determine whether any association existed between errors and the occurrence of paroxysmal activity during a particular trial. Because the level of task difficulty (sequence length) was adaptive giving a 50 per cent error rate, most of the testing involved only 2 or 3 sequence lengths. Separate 2 × 2 contingency tables were drawn up for each sequence length, showing the incidence of correct or incorrect trials with or without epileptiform activity. For each table with a determinate association (i.e. with all marginal totals greater than zero) χ^2 was then calculated without correction for continuity according to the conventional formula $(O-E)^2/E$. The square root of the value of χ^2 for each table yielded a value of z, which was given a sign corresponding to that of any association between error and discharge. The values of z were then summated and the sum divided by the number of values contributing to the sum. This provided a new value of z from which a probability level was obtained. The strength of association was estimated by calculating the mean value of Yule's coefficient of association.

RESULTS

Forty-six patients were testable; their principal clinical characteristics are summarized in Table 1.

The effects of testing on discharge frequency are summarized in Table 2. In 7 patients there was an increase in discharge incidence. As none of these patients was photosensitive, there is no reason to suppose that exposure to the TV monitor as such was responsible for this effect. One patient became untestable, showing no trials without epileptiform activity, so the control condition of no discharge could not be tested. Another (not included in Table 2) developed myoclonic jerks and therefore no longer fulfilled the admission criteria for the study. In 28 there was no change and in 16 there was a decrease. However, in only 4 of these 16 was the suppression so marked as to render statistical analysis impossible. In 2 patients there was a change in the morphology of the discharges during the task. In both cases the spikes disappeared and slow waves remained.

TABLE 1

Age Mean 25 ± 11, range 10 to 46 yrs	
Sex Male/Female 26/20	
Type of epilepsy	
Primary generalized	3
Partial	20
Secondary generalized	18
Unclassified	5

In analysing the test results, it seemed appropriate to employ more stringent statistical criteria for research than for clinical purposes. An association of error with epileptiform activity was accepted as evidence of TCI for the management of an individual patient at a significance level of 0.1 (for a one-tailed test). By this criterion, TCI was demonstrable in 11/22 patients with focal or asymmetrical discharges and in 13/24 with symmetrical generalized epileptiform activity (Table 3). For a more detailed analysis for research purposes a 0.05 level on a two-tailed test was regarded as significant. This criterion was satisfied by 7/22 patients with focal or asymmetrical epileptiform activity and by 9/24 with symmetrical discharges.

In Table 3 data for patients with generalized epileptiform activity that had a unilateral predominance have been grouped with the data for patients exhibiting focal activity on the same side. Nine of the 12 patients with left-sided activity who were tested on both the verbal and topographic tasks showed a stronger association between errors and epileptiform activity for the verbal task than for the topographic. The association between epileptiform activity and errors on the verbal test reached significance in 3 of the 14 patients.

The opposite pattern obtained for 4 of the 5 patients with right-sided epileptiform activity who were tested on both tasks. In 3 of the 6 patients who received the topographic test the association between errors and epileptiform activity reached significance. The single patient with a significant positive association of right-sided focal discharges and errors on the verbal task was left-handed.

For patients with symmetrical generalized epileptiform activity (Table 3B) the pattern of results was midway between the extremes obtained for patients with asymmetrical discharges. For the majority of those patients who performed both tests (12/16) the association between errors and epileptiform activity was stronger for the topographic test. For the remaining patients the reverse was the case. In 7/23 patients the association reached significance on the topographic test, as compared with 3/17 on the verbal test. In one patient the association was significant on both tests.

TABLE 2. SEIZURES AND DISCHARGE RATE DURING TESTING

Eliminated because of seizures during testing	2
Change in discharge rate	
Increase, testable	6
untestable	1
No change	28
Decrease, testable	12
untestable	4
Total patients	51
Patients testable	46

The effect of the degree of asymmetry and its lateralization on the strength of the association between errors and epileptiform activity is summarized in Table 4. In patients with asymmetrical discharges, the association between greater impairment of the verbal task and lateralization of the discharges to the presumed dominant hemisphere is significant ($P < 0.02$ by Fisher's exact probability test, two-tailed).

The preceding results were based on a comparison of error rates in trials with or without paroxysmal activity, regardless of the timing of the discharges. Table 5 presents a more detailed analysis of the relationship between errors and the occurrence of discharges at different points in each trial: within 2 s prior to the stimulus, during stimulus presentation, during the interval between stimulus and response, during both stimulus and response, during response and within 2 s after completion of response. These categories are mutually exclusive: discharges during the stimulus are taken to include those commencing earlier or continuing into the stimulus response interval, and discharges during the response include those commencing in the stimulus response interval or continuing after the response. Only error rates differing from the basal interdischarge level are shown; ties are excluded, as are missing data (due to the nonoccurrence of discharges in a particular phase of

TABLE 3A. PATIENTS WITH FOCAL AND ASYMMETRICAL GENERALIZED PAROXYSMAL EEG ACTIVITY

Paroxysmal activity		*Topographic task*		*Verbal task*	
Distribution	*Type*	*Mean Yule's coefficient of association*	*z*	*Mean Yule's coefficient of association*	*z*
Focal right					
	S-W	0.22	2.79**	−0.80	−1.37
	S-W	0.24	2.45*	0.17	1.06
	Sp	0.30	0.34	0.88	2.44**
	S-W	0.2	1.52†	0.19	1.06
	S-W	0.33	2.05*	—	—
Generalized right maximal					
	T	0.07	0.53	−0.02	−0.28
Focal left					
	S-W	0.50	0.52	0.27	0.49
	T	−0.26	−1.47	0.44	0.21
	D	−0.29	−0.81	0.53	2.01*
	S-W	0.20	0.58	−0.16	−0.17
	Sh	0.09	0.54	0.21	0.64
	S-W	—	—	1.0	1.49†
	T	0.16	0.44	1.0	0.35
Generalized left maximal					
	T	−0.41	−1.20	−0.18	−0.16
	S-W	−0.11	−1.32	0.49	1.36
	S-W	0.79	1.85†	−0.57	−0.85
	S-W	0.25	0.37	0.50	1.29
	S-W	0.21	1.16	0.75	2.81**
	S-W	0.19	1.46†	0.82	3.60**
	S-W	0.52	1.02	—	—
	S-W	1.0	1.67†	—	—
	S-W	—	—	0.22	−0.45

the trials in some individuals). The error rate when discharges occurred during the stimulus is also compared with that observed when paroxysmal activity coincided with the response. Significance of any apparent effects was evaluated by the sign test (two-tailed).

It will be seen that the error rate associated with discharges during the stimulus was strikingly higher than the basal level ($P < 0.001$) and than that when discharges occurred during the response ($P < 0.002$). Indeed paroxysmal activity during response did not produce any apparent increase in errors. Intermediate effects are seen with discharges in the stimulus response interval or continuing from

TABLE 3B. PATIENTS WITH SYMMETRICAL GENERALIZED PAROXYSMAL EEG ACTIVITY

Paroxysmal activity	*Topographic task*		*Verbal task*	
Type	*Mean Yule's coefficient of association*	*z*	*Mean Yule's coefficient of association*	*z*
S-W	0.30	0.01	0.14	1.49†
T	−0.20	−0.16	−0.07	−0.81
S-W	1.0	1.49†	0.22	0.69
S-W	0.48	0.35	0.12	0.03
D & T	1.0	2.85**	−0.43	−1.09
T	0.29	0.47	0.22	0.64
S-W	0.90	1.51†	0.89	3.34**
S-W	−0.63	−0.44	0.05	0.33
S-W	−0.26	−1.00	−1.0	−1.00
S-W	0.58	2.86**	0.55	2.37*
S-W	0.78	2.00*	0.31	0.08
D	Excessive increase in PA		0.66	0.34
S-W	−0.35	−0.26	0.2	2.82**
S-W	0.71	3.48**	0.23	0.64
D	0.16	0.57	0.08	0.13
S-W	0.29	0.28	0.58	0.17
S-W	0.5	0.44	0.47	0.864
S-W	−0.38	−0.33	—	—
S-W	1.0	−1.80	—	—
S-W	0.80	4.07*	—	—
S-W	1.0	2.64**	—	—
S-W	−0.37	−0.04	—	—
S-W	0.20	1.64†	—	—
S-W	1.0	3.64**	—	—

Key to types of paroxysmal activity. S-W = spike-wave. Sp = spikes. T = theta bursts. D = delta bursts. Sh = sharp waves.

† $P < 0.1$ single-tailed (positive associations only). * $P < 0.05$ two-tailed. ** $P < 0.01$ two-tailed.

TABLE 4. ASSOCIATION BETWEEN ERRORS AND EPILEPTIFORM ACTIVITY

Epileptiform activity	*Greater on topographic task*	*Greater on verbal task*
Right-sided	4	1*
Symmetrical	12	4
Left-sided	3	9

* Left-handed patient.

TABLE 5. ERROR RATES

	Discharge during			
	Topographic task		*Verbal task*	
	Less	*Greater*	*Less*	*Greater*
Error rate relative to interdischarge level				
2 s before stimulus	12	21	19	6 $P < 0.02$
Stimulus	8	34 $P < 0.001$	6	24 $P < 0.01$
Stimulus-response interval	11	22 $P < 0.1$	10	19
Stimulus and response	6	13	13	13
Response	18	16	15	16
2 s after response	8	10	5	2
Error rate relative to that when discharge occurs during response				
Stimulus	7	27 $P < 0.002$	6	20 $P < 0.02$

the stimulus through to the response. There appears to be an increased error rate (not significant) with discharges in the 2 s prior to the topographic stimulus; however, the opposite effect is observed with the verbal task. Otherwise the two tests give similar results.

Finally, the clinical context of TCI will be illustrated by two examples.

Case History 1

A 35-year-old male librarian had an excellent academic record up to the age of 18. However, when he attempted to read law at university he became subject to an inability to concentrate which forced him to abandon his studies. He continued to have the same difficulties in his work as a librarian. When stressed, he could not answer reader's enquiries and had particular difficulty in cataloguing. A psychological examination suggested that his problems were due to obsessionality; at one time a diagnosis of schizophrenia was considered. The possibility of epilepsy first arose when an ENT surgeon astutely noted that a letter from the patient contained repeated hesitations, where the writing trailed away. A decision to carry out EEG and video monitoring in combination with performance tests was made more in the expectation of excluding than of establishing an epileptic basis for his complaints. Indeed, during a period of 5 h monitoring without intellectually demanding activities no EEG abnormality was observed. However, during the performance of the topographic task, generalized 3 Hz spike-wave discharges appeared, their duration increasing with task difficulty. During these discharges no obvious ictal behavioural changes were observed apart from an inability to continue the task and some evident perplexity which continued 10 s or more after each discharge. He was treated with sodium valproate (1800 mg daily) which was followed by a marked improvement in his complaints of poor concentration and a striking reduction of epileptiform EEG activity during performance testing.

Case History 2

A 13-year-old boy complained of difficulty with his school work. The EEG contained repeated runs of generalized sharp waves or irregular spike-wave activity maximal in amplitude over the frontal regions. Both the topographic and the verbal task showed significant ($P < 0.01$) transitory cognitive impairment. Due to the repeated errors associated with the EEG discharges he never advanced beyond a series length of 2 blocks or 2 words. Diazepam (7.5 mg) was then administered by slow intravenous injection, suppressing the epileptiform activity. After 15 min performance testing was repeated.

Although the patient was now extremely drowsy the EEG contained no epileptiform discharges and he repeatedly achieved two consecutive correct responses to series of 3 blocks. An hour later he was again tested. Epileptiform activity was still absent, he was less drowsy and responded correctly to series of up to 4 blocks. Sodium valproate (900 mg daily) was prescribed; his school work improved, but a year later he relapsed with frequent overt absences.

DISCUSSION

The tests described appear to satisfy the main requirements for a means of investigating TCI as a routine clinical service. Of those 51 patients who had sufficient discharges under control conditions for testing to be attempted, 90 per cent were both willing to perform the tasks for an adequate period of time and exhibited a sufficient discharge rate to permit a conclusion concerning the presence or absence of TCI demonstrable by these tests. Behaviour was monitored by video recording and subjects exhibiting overt seizures during the investigation were excluded. This implies that selection was more rigorous than in most, arguably all, previous studies. Nevertheless, TCI was established with a frequency similar to that generally reported by other authors. Cognitive impairment was demonstrable with 10 per cent confidence in 50 per cent of patients overall: in 50 per cent of those with symmetrical and 40 per cent with asymmetrical generalized discharges, and in 58 per cent of those with focal epileptiform activity. This finding was unexpected: the occurrence of TCI during generalized discharges is well documented but its presence during subclinical focal epileptiform activity has, so far as we are aware, been suggested only by Kooi and Hovey (1957). Tuvo (1958), Prechtl *et al.* (1961), Sellden (1971) and Hutt *et al.* (1977) found no evidence of TCI during discharges variously described as unilateral, focal or localized. An association of increased reaction time with localized increase in low frequency components of EEG power spectra has been demonstrated, however, by Stevens *et al.* (1972), and these 'ramp spectra' in turn were associated with spiking at depth electrodes.

The effects of focal discharges were specific to the task lateralized to the appropriate hemisphere. This suggests that TCI is not necessarily a consequence of a general impairment of attention but can reflect disruption of specific psychological functions located in the region or regions where the epileptiform discharges arise. The selective nature of the impairment further suggests the possibility that when TCI was not demonstrable by the present tests, the discharge involved structures different from those affected when TCI was found. Effects of these discharges too might have been detected by different tests.

The practical clinical importance of TCI during focal discharges is uncertain. The small numbers of subjects with focal discharges in the present series (despite the fact that some 70 per cent of patients attending the Instituut have partial epilepsy) reflects a low incidence within and between subjects of focal interictal epileptiform activity in the eyes open, alert state. This in turn may suggest that very few patients with only focal interictal discharges will suffer any important disability due to TCI. The finding of impairment during focal discharges, does, however, have other, practical implications for the use of psychological testing in patients undergoing surgical treatment of partial epilepsies. Corsi's block-tapping test, for instance, was specifically used for evaluating pre- and postoperative memory deficits (Milner, 1971), apparently on the assumption that these reflected anatomical lesions, not paroxysmal dysfunction. The interpretation of the results of such testing may be difficult if there are frequent interictal discharges in either the pre- or postoperative EEG. The association between lateralization of epileptiform activity and the verbal or nonverbal nature of the TCI that it produces may further confuse the assessment. The patient may trade a selective cognitive deficit, due to a focal dysfunction, for a qualitatively similar impairment produced by the operative lesion.

In accordance with the findings of previous workers, the morphology of the paroxysmal activity was an important determinant of TCI (fig. 1). Ten patients were included with paroxysmal delta or theta bursts without frank spikes or sharp waves and only 2 exhibited evidence of TCI. If these subjects are excluded, then the incidence of TCI in the remaining 36 with epileptiform activity was 61 per cent. It

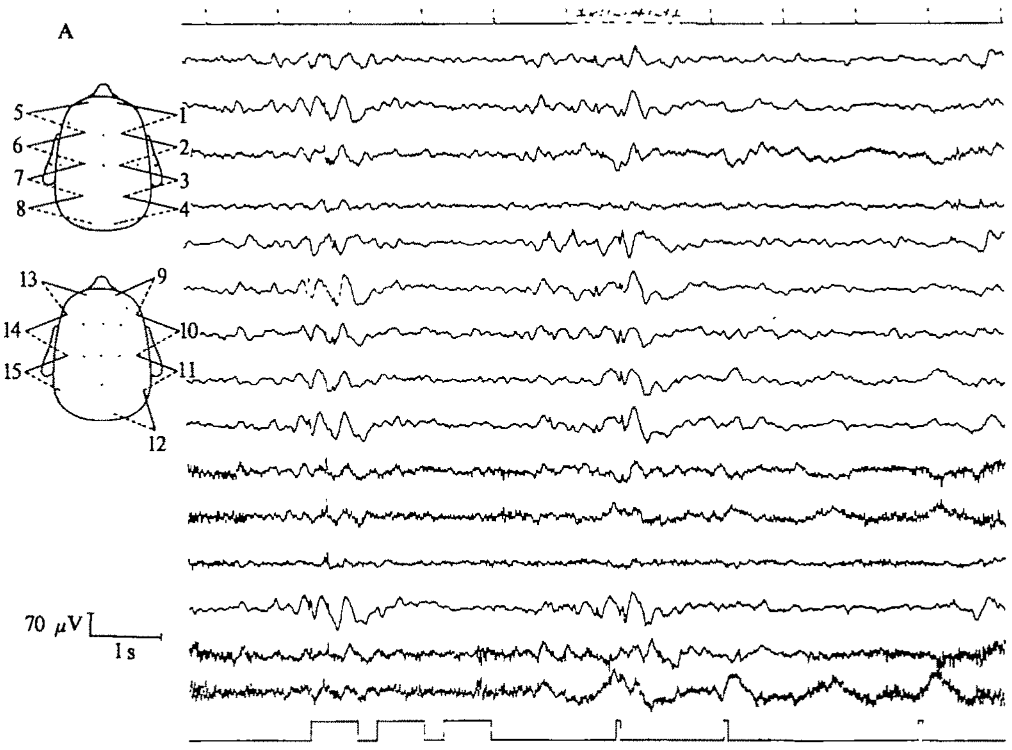
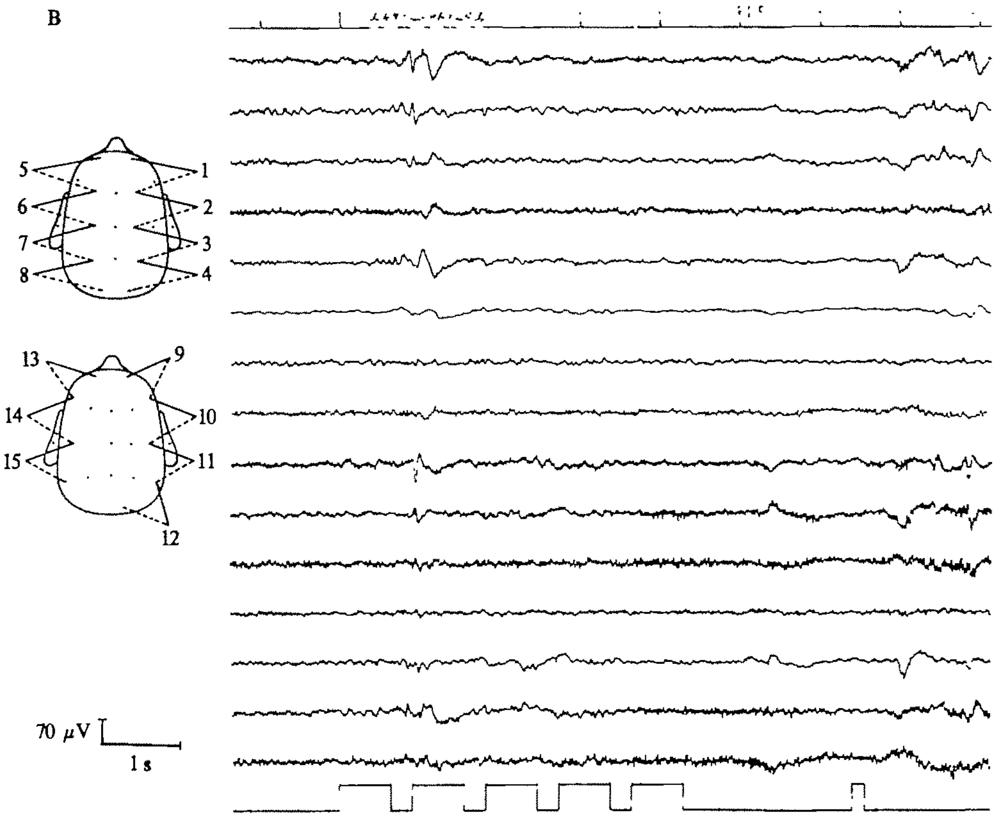


FIG. 1. Epileptiform discharges during performance testing. A, generalized asymmetrical spike-wave discharge in a subject showing no evidence of TCI. The marker channel (16) indicates the stimuli (each large square-wave corresponds to presentation of a block) and correct responses (short pulses). B, (p. 305), focal right-sided discharge in a subject demonstrating TCI on the topographic task. A single incorrect response is indicated by a wider pulse. Time constant 0.3 s, HF response 30 Hz for both A and B.

should further be noted that the Instituut is a centre of third referral: patients with typical petit mal absences are rarely seen in our EEG Department and had moreover been excluded by the selection of subjects without overt seizures during their EEG discharges. Of the 19 patients with symmetrical spike and wave activity, none exhibited those 'classical' regular 3 Hz discharges which previous authors have shown to be most strongly associated with TCI.

It is interesting that the effects of epileptiform activity were greatest when the activity occurred during the presentation of the stimuli. One possible reason for the selective nature of the disruption might be that the presentation of the stimuli was paced, whereas the production of responses was not. Another possibility is that this result is an expression of the more general finding that a concurrent task during stimulus presentation produces a greater effect on errors than one during recall (A. Baddeley *et al.*, in preparation). Discharges during the stimulus could disrupt attention or perception or interfere with 'working-memory' as suggested by Hutt and Gilbert (1980).



The case histories cited indicate that some people suffer a clear social disadvantage as a consequence of TCI and may be benefitted by antiepileptic medication intended to suppress the discharges. It would be regrettable, however, if the present findings were in any way considered to justify the practice of treating EEGs rather than patients. The advice of Browne *et al.* (1974) that 'therapy should be aimed at suppressing all spike-wave paroxysms' may prove to be correct, but is premature. It has yet to be determined what proportion of all patients exhibiting subclinical discharges are significantly handicapped due to TCI. Further work will also be required to establish in how many the possible benefits of antiepileptic drugs to suppress the discharges, or of appropriate counselling to take account of the consequences of TCI, outweigh respectively the side-effects or the social disadvantages of such management. A necessary preliminary to further research was the development of an appropriate method for detecting TCI in routine clinical EEG practice and this, we suggest, has now been achieved.

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VISUAL PROCESSING DEFICITS AS ASSESSED BY SPATIAL FREQUENCY CONTRAST SENSITIVITY AND BACKWARD MASKING IN NORMAL AGEING AND ALZHEIMER'S DISEASE

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SUMMARY

Visual functions of patients with senile dementia of the Alzheimer type were compared with those of young people and age-matched controls. Visual acuity and spatial frequency contrast sensitivity did not differ significantly between Alzheimer patients and normal elderly subjects, although both were impaired in comparison with young subjects. Alzheimer patients required more time than ageing controls to identify letters and were susceptible to the interfering effects of a backward pattern mask on letter recognition over a longer interval. The spatial extent over which the pattern mask was effective, as well as the time interval over which a homogeneous mask interfered with letter recognition, were equivalent in normal old people and Alzheimer patients. In all the masking tasks, young people performed better than the old. It is suggested that Alzheimer's disease affects later central visual functions more than early relatively peripheral ones.

INTRODUCTION

Recent interest in the behavioural deficits accompanying Alzheimer's disease has focused almost exclusively on memory, language, and other cognitive functions (*see* Katzman *et al.*, 1978; Schwartz *et al.*, 1979; Corkin, 1981; Bayles, 1982). To our knowledge, there has not been a single published study on sensory and perceptual function in Alzheimer's disease. This is all the more surprising since Alzheimer patients or their families often complain spontaneously of perceptual problems and the neuropathology associated with Alzheimer's disease affects structures (such as secondary or association cortex) believed to mediate higher-order perceptual functions. This paper is the first to document the effects of Alzheimer's disease on some visual functions.

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Brain atrophy, senile plaques, and neurofibrillary degeneration appear to be the histopathological changes most relevant to the dementia of the Alzheimer type (Tomlinson *et al.*, 1970). Brain atrophy is a result of both neuron loss and reduction in neurocytoplasmic volume, but does not necessarily correlate with the degree of intellectual impairment observed in an individual (Blessed *et al.*, 1968; Tomlinson *et al.*, 1968). Both senile plaques and neurofibrillary degeneration, however, correlate with the presence of dementia in ageing individuals. Recent work with animals (Crapper, 1973; Crapper and Dalton, 1973*a*, *b*; Crapper and Tomko, 1975) and in man (Ball, 1976, 1977) suggests that neurofibrillary degeneration is a particularly important correlate of intellectual decline in Alzheimer's disease, although the exact functional significance of this characteristic histopathological change is unknown.

The effects of these degenerative processes on perceptual functions have not been investigated. In Alzheimer's disease, neurofibrillary degeneration occurs throughout most of the cerebral cortex and limbic structures. These changes occur most frequently in the large pyramidal shaped cells of the hippocampus and of layers III and V of the association areas of cerebral cortex (McMenemey, 1963; Tomlinson *et al.*, 1968, 1970), but are absent in the geniculostriate system up to and including area 17 (primary visual cortex) (Schenk, 1955; Crapper, 1974, 1976). In contrast, senile plaques are more uniformly distributed throughout the visual cortex (Crapper *et al.*, 1975). This pattern of degeneration suggests that some visual functions, such as early low-level processes associated with the geniculostriate system might be spared in Alzheimer's disease, and others, such as those later higher-order processes mediated by structures central to the striate cortex, might be impaired in Alzheimer's disease. The major purpose of this paper, therefore, is to document some aspects of visual perception in Alzheimer patients and, if possible, to relate our findings to the degenerative processes associated with the disease.

Of the many tests at our disposal, we first chose to look at visual acuity, spatial frequency contrast sensitivity, and susceptibility to visual masking. For reasons that will become apparent, we considered that these tests would illustrate the range of visual functions that are spared and impaired in Alzheimer's disease.

EXPERIMENT 1. ACUITY AND CONTRAST

Testing acuity by traditional methods seemed a logical first step. We chose to examine spatial frequency contrast sensitivity because it provides a different test of spatial resolution in that it can specify which part of the spatial frequency domain is most severely affected by the disease. Spatial frequency is defined as the number of alternating pairs of black and white regions (sinusoidal gratings) per degree of visual angle. It is now generally accepted that visual input is processed along various spatial frequency channels of unequal sensitivity. Under ideal conditions humans can distinguish gratings of spatial frequencies between 0.5 to 50 c/deg from a uniform grey stimulus, the greatest sensitivity occurring at 2 to 4 c/deg (Cornsweet, 1970; Campbell, 1974; Lennie, 1980).

It is also widely believed, but not universally held, that low spatial frequencies are processed by a system whose characteristics are distinct from that involved in processing high spatial frequencies and that each system subserves different perceptual functions (Lennie, 1980; Graham, 1981). This dissociation suggests that neural damage could selectively affect one system but not the other. There have been a number of reports of loss of sensitivity restricted only to some spatial frequencies in patients with various disorders of the visual system but with normal or near normal Snellen acuity (Bodis-Wollner, 1972, 1977; Bodis-Wollner *et al.*, 1978; Regan *et al.*, 1977, 1981; Zimmern *et al.*, 1979). For example, Regan *et al.* (1977, 1981) found that patients with multiple sclerosis had a loss of sensitivity for low and/or intermediate spatial frequencies, whereas Bodis-Wollner (1972) found that patients with striate cortex lesions had reduced sensitivity primarily to high spatial frequencies. In Alzheimer patients the striate cortex is relatively spared from the degenerative effects of the disease, but the prestriate and posterior temporal and parietal lobes are not. It would be particularly instructive, both theoretically and practically, to know whether spatial frequency contrast sensitivity is affected by diffuse damage to these extrastriate structures and, if it is, whether all channels are affected equally.

Subjects

Three subject groups were examined: (1) a young control group consisting of 11 individuals aged 20 to 29 yrs (mean 25 yrs; (2) a control group of 11 nondementing persons aged 53 to 77 yrs (mean 63), who were either fully employed or were still active in the community; and (3) a group of 10 individuals with the clinical diagnosis of Alzheimer's disease aged 53 to 75 yrs (mean 64). Verbal IQ of the patients at the time of testing ranged from 57 to 128 with an average of 80.4. Performance IQ, except for one patient who was untestable, ranged from 55 to 111, with an average of 75.6. The full scale IQs for the testable patients ranged from 50 to 121, with an average of 87.1. The clinical diagnosis of Alzheimer's disease in this study was based on a careful process of elimination. Relatively slow intellectual decline, highlighted by impairment of memory functions, in the presence of marked cerebral atrophy, evidenced on either a pneumoencephalogram or CT brain scan, were critical diagnostic indices. In addition there was no evidence of space-occupying lesions, nor of rapid deterioration of motor function or basic personality traits. In a separate study, D. Crapper-McLachlan (unpublished observations) found that of patients diagnosed as Alzheimer's disease by these criteria, 86 per cent proved to have the characteristic neuropathology of this disease at autopsy.

From the original group of 10 individuals with Alzheimer's disease, 6 were capable of reliable performance on the spatial frequency contrast threshold procedure. The failure of the remaining 4 subjects to perform reliably was due more to their inability to comprehend and follow instructions than to their poor visual function. Nonetheless, the average IQ of these patients was similar to the group average. All subjects were successfully tested on the visual masking procedures (*see below*). Aside from the neurological disorder of Alzheimer's disease, all subjects were in good health and had a corrected visual acuity of 20/40 (Snellen) or better. Informed consent was obtained from all the subjects or members of their family.

Procedure

The effects of normal ageing and Alzheimer dementia on primary visual function were tested by measurements of visual acuity and spatial frequency contrast sensitivity.

Visual acuity. A Bausch and Lomb Master Ortho-Rater was used to measure visual acuity. The acuity scores were maintained in Ortho-Rater format for analysis (Ortho-Rater 10 = 20/20, Snellen; Ortho-Rater 5 = 20/40, Snellen).

Spatial frequency contrast sensitivity. Contrast is defined as the ratio of the difference between the regions of highest and lowest luminance and the sum of these luminance intensities ($c = I_{max} - I_{min}/I_{max} + I_{min}$). The amount of contrast required to detect the presence of a particular spatial frequency grating defines the contrast threshold for that spatial frequency. In this study, contrast thresholds were determined for six different spatial frequencies, 0.5, 1, 2, 4, 8, and 12 c/deg. The 'sine-wave' gratings were produced using methods similar to those described by Campbell and Green (1965). Two Heath Company signal generators were used to drive the Y and Z axes of a Tektronix 502A oscilloscope. After setting the time base to sweep the width of the screen 200 times per second, a 1000 line raster was generated by applying a 200 kHz triangular waveform signal to the Y-axis. Modulation of the Z-axis was accomplished by applying a sine-wave signal from the second signal generator to the CRT imput. Luminance was linearly related to Z-axis voltage. Spatial frequency of the resulting grating was manipulated by varying the frequency output of the Z-axis signal generator. The intensity control at the front of the oscilloscope was used to adjust the luminance of the raster. Z-axis modulation varied the intensity of the raster equally above and below this baseline, therefore maintaining the mean luminance of the gratings at a level equal to the unmodulated raster. The amplitude of the signal generator output driving the Z-axis was measured on a digital voltmeter. Directly (2.54 cm) in front of the CRT face was a 30 cm square field of white bristol board. There was a 5 cm square opening in the centre of this white field forming a visual angle of 4 deg through which the subject viewed the sine-wave gratings binocularly from a distance of 73 cm. For all gratings, the overall mean luminance level was maintained at 5 cd m^{-2}. The surround field was matched both in colour and luminance to the central raster by chromatic lighting with filtered, variable intensity incandescent light sources. The target gratings were presented intermittently for a duration of 1 s alternating with a 1 s presentation of a uniform background.

The subject was seated comfortably in a darkened room, illuminated only by the light sources used to maintain the luminances of the surround field. The subject's head was positioned securely by a Bausch and Lomb chin rest and head restrainer. After familiarizing the subject with each of the spatial frequency gratings at moderate contrast levels, contrast was set to zero and the detection trials were begun. The six spatial frequencies were presented in pseudorandom order a total of five times. Once a grating was chosen by the experimenter, the subject was instructed to begin attending to the target field. Constrast was then increased by a constant 0.003 contrast units every 2 s (1 cycle of alternation between grating and background) until the subject reported detection of a grating. As a check of response reliability, the subject was asked to report the relative size of the detected grating ('wide', 'medium' or 'fine'). If this report was not accurate, the trial would be repeated later in the session. The criterion for accurate report of the spatial frequency required the subject to assign the following spatial frequency gratings to the designated category: 0.5, 1, 2 ('wide'); 2, 4, 8 ('medium'); 4, 8, 12 ('fine'). Ten erroneous reports excluded the subject from the study. The contrast sensitivity for each spatial frequency was defined as the inverse of contrast threshold averaged over the five trials. A plot of contrast sensitivity *vs* spatial frequency generates a spatial-frequency contrast-sensitivity function.

Results and Comment

The young control group had a mean acuity of 10.6 ± 1.4 (Ortho-Rater). The normal ageing and Alzheimer's disease groups were similar to each other with acuities of 7.8 ± 1.5 and 8.3 ± 1.2, respectively. As expected, the two older groups had slightly but significantly ($P < 0.05$) poorer visual acuity than the younger group.

The spatial frequency contrast functions for each group were identical in form

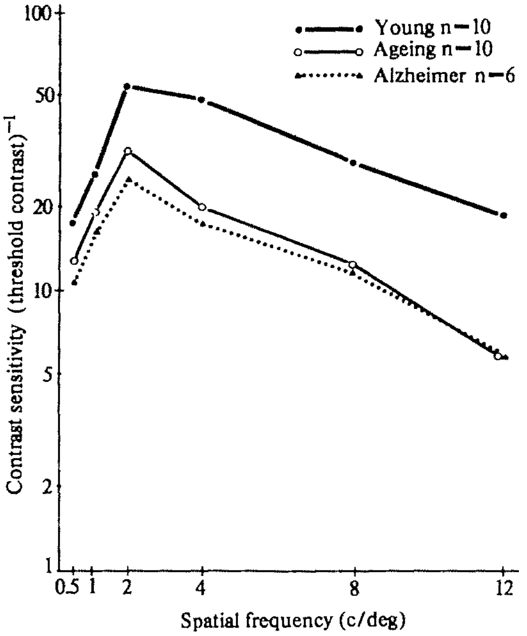

FIG. 1. Spatial frequency contrast sensitivity function for young, ageing and Alzheimer groups.

(fig. 1), yielding a significant main effect for spatial frequency (F(5,125) = 18.9, $P < 0.01$). However, the young control group had significantly greater sensitivity (ANOVA, F(2,23) = 19.5, $P < 0.01$) at all spatial frequencies except 2 c/deg as indicated by *post hoc* Newman-Keuls tests. No significant differences were found between the ageing control and Alzheimer groups. Ageing leads to reduced optical transmission and increased light scatter due to changes in the lens, humours, and pupil size (Said and Weale, 1959; Birren, 1960; Ruddock, 1965; Corso, 1971), as well as loss of granule cells in the primary visual cortex (Brody, 1955, 1976) and may account for the observed decrease in sensitivity in the elderly (Bodis-Wollner, 1972, 1977). These processes, however, seem not to be accelerated by Alzheimer's disease. The results are consistent with neurohistological studies (Schenk, 1955; Tomlinson *et al.*, 1968, 1970) and radiological evidence from PET scans (Benson *et al.*, 1981) that the striate cortex is not more severely affected in Alzheimer's disease than in normal old people. Lastly, the results suggest that damage to extrastriate cortical visual areas do not noticeably influence spatial frequency contrast sensitivity.

It should be noted that our results are somewhat at variance with those of Sekuler and Hutman (Sekuler and Hutman, 1980; Sekuler *et al.*, 1980; Hutman and Sekuler, 1980) who found that old people had reduced sensitivity only at low and intermediate spatial frequencies but were normal at frequencies of 16 c/deg, and presumably higher. This is surprising given the increased light scatter in the ageing eye which would most affect the high spatial frequencies. Be that as it may, the source of the discrepancy between our study and theirs is difficult to ascertain because the studies differed in so many ways. First, the average age of their subjects was ten years older than ours; secondly, their stimuli flickered at 0.33 and 6 Hz whereas ours flickered at 1 Hz; thirdly, they measured threshold by approaching it from above and below whereas we approached it only from below; fourthly, the overall luminance of their grating was higher than ours by a factor of 10.

It is most likely that one of the last two differences was critical. Old people may adopt a different criterion from younger individuals in deciding when a grating is visible and these criterion differences may exert a greater influence on threshold detection when threshold is approached from only one direction. Against the idea that criterion differences account for the discrepancy between our study and those of Sekuler and Hutman is the fact that Alzheimer patients, who are demented and often behave inappropriately, nonetheless behaved similarly to old people on this test. If criterion differences were at work, we would expect significant differences between the old and the Alzheimer patients, but no such differences were found.

The most likely explanation is that overall luminance differences of the gratings were the source of the discrepancy. It is possible that at low luminance, differences between old and young people would emerge at high spatial frequencies. Because our study was completed (Schlotterer, 1977) and reported (Schlotterer *et al.*, 1978) before that of Sekuler and Hutman, we were in no position to replicate their findings. We plan, however, to investigate these ideas in future work. We are encouraged that subsequent work by Sekuler and his colleagues (Owsley, 1982; Sekuler and Owsley, 1982) has yielded results more consistent with our own and with the known optical properties of the aged eye, namely, that sensitivity to high spatial frequencies is decreased.

Whatever the source of the discrepancy, the finding of primary interest is that the Alzheimer patients who were sufficiently alert to complete the task were no worse than their age-matched controls on tests of spatial frequency contrast sensitivity. One reason for this may be that spatial frequency analysis is a relatively low-level visual function that is dependent primarily on early stages of visual processing. If this is true, other functions that are similarly dependent on early stages of processing should also be intact in Alzheimer patients, whereas those functions that are dependent on later higher-order stages should be impaired. The second experiment was designed to explore this possibility.

EXPERIMENT 2. BACKWARD VISUAL MASKING BY SUPERIMPOSITION OF A HOMOGENEOUS AND A PATTERNED STIMULUS

Visual masking occurs when a stimulus interferes with the perception of a temporally contiguous target. In the typical backward masking paradigm, the onset of a briefly presented target precedes the onset of the interfering mask. Target perception may be perfect without the mask but it can drop to zero at optimal temporal separation between the mask and target. As the interval between the onset of the target and the onset of the mask increases (stimulus onset asynchrony or

SOA), the target gradually escapes the effects of the mask until perception is once again perfect. This interval is known as the critical SOA.

Backward visual masking can involve both peripheral and central processes (Turvey, 1973; Breitmeyer and Ganz, 1976; Michaels and Turvey, 1979; Felsten and Wasserman, 1980). If the mask is a homogeneous stimulus without contours, it interferes with the target if it is presented to the same eye as the target. Because a homogeneous stimulus is not an effective mask when it is presented to the eye opposite to the target, it is presumed to act peripherally, prior to the point at which inputs from the two eyes converge. This convergence first occurs in the striate cortex (Hubel and Wiesel, 1968), but is found more extensively in the prestriate cortex and beyond (Zeki, 1978). Because the geniculostriate system up to and including the striate cortex is relatively spared in Alzheimer patients, we expect them to show normal masking functions when a homogeneous mask is used.

If the mask is patterned such that it has contours similar to those found in the target, then the mask is effective even when it is presented to the eye opposite to the target. This dichoptic interaction suggests that backward masking with patterns is also a central phenomenon that occurs at higher-order stages of processing where inputs from the two eyes interact. If the critical interaction for backward pattern masking occurs beyond the striate cortex, then Alzheimer patients should react abnormally to backward pattern masks. The results of our study confirmed our predictions regarding the performance of Alzheimer patients on tests of backward masking with both a homogeneous and a pattern mask.

Subjects

Ten young controls whose average age was 25 yrs, 11 ageing controls whose average age was 64.1 yrs and 10 patients with Alzheimer's disease whose average age was 64.0 yrs, served as subjects in the experiment.

Procedure

The targets were letters and the masks were either a flash of light or a meaningless pattern. A Pandora's Box 3-channel tachistoscope was used to present visual stimuli to both eyes at an optical distance of 1 m. The target consisted of 9 symmetrical letters of the alphabet (A, H, O, T, U, V, W, X, Y) constructed from 1.25 cm Franklin-Gothic style Quik-Stik lettering and subtending a visual angle of 0.7 to 1.0 deg square depending on the letter. Each target was positioned centrally in a 5 cm (2.9 deg) square field which overlapped with the apparent location of the target field. The patterned mask consisted of an overlapping Franklin-Gothic letter 'I' and segments of the letter 'T' cross-bars that subtended a visual angle of 1.2 deg square within a 2.9 deg square blank field. All masks were exposed for 30 ms at a constant luminance of 170 cd m^{-2}. For the purpose of light adaptation and target localization, the 2.9 deg square blank fixation field was provided. This field was illuminated whenever the target or masking fields were not present. In the centre of this dimly illuminated (4 cd m^{-2}) field was located a small black point (1 mm diameter) which corresponded to the apparent centre of the target stimuli. Five minutes of adaptation at the reduced luminance of the fixation field preceded actual testing. During this period the subject was completely familiarized with the target stimuli and testing procedures. The interval between the onset of the target and the onset of the masking stimulus is defined as the stimulus-onset asynchrony (SOA). The SOA at which the target escapes the effects of the mask defines optimal performance.

After an adaptation period, the subject was asked to identify each letter as it was presented in the centre of the fixation field. The nine target stimuli were randomly chosen for each trial. The first stimulus was presented beginning with a target duration of 1 ms. If the subject responded correctly, a new target was chosen and presented at the same target duration. Following each error, the target stimulus was changed and 1 ms was added to the target duration. This procedure continued until the subject correctly identified four targets in a row. The target duration at which this was accomplished is defined as the target-duration threshold.

All masking procedures were carried out with the time between the termination of the target and the onset of mask (interstimulus interval, ISI) equal to zero ms. An initial value of target duration was chosen for each subject which was equal to the target-duration threshold. Randomly chosen letters were then presented at this duration and were followed immediately by a 30 ms mask. If the subject failed to report the target correctly, the duration was increased in 2 ms steps. If the subject succeeded in identifying four targets in a row correctly, the existing value of the target duration was noted. Because the ISI was equal to zero, this critical value of target duration was equivalent to SOA for that mask. This value was determined three times for each mask with the average of the last two values being used in the final analysis.

Results

The minimum time required to identify a constant luminance target (target duration threshold) varied for each of the three groups. The youngest group required 4.3 ± 1.0 ms which differed significantly from the ageing control group who required 8.1 ± 5.1 ms ($F(1,19) = 5.18$, $P < 0.05$), which differed significantly from that of Alzheimer patients who required 16.0 ± 10.2 ms ($F(1,19) = 5.20$, $P < 0.05$). The critical SOA derived for both the flash and pattern masks is represented in fig. 2. The ageing controls differed significantly from the young both in the homogeneous flash mask condition ($F(1,19) = 21.1$, $P < 0.01$) and in the pattern mask condition ($F(1,19) = 18.8$, $P = 0.01$). The Alzheimer patients differed from ageing controls only in the pattern mask condition ($F(1,19) = 18.53$, $P < 0.01$), but not with homogeneous flash condition ($F(1,19) = 1.23$). When covariate adjustments for visual acuity were made for the young and ageing controls, the significant differences between them in the pattern and flash mask condition were removed. Since there were no significant differences in acuity between the ageing control and dementia groups, covariate adjustments for these groups cannot be made.

Comment

The results are clearly consistent with the predictions that Alzheimer patients would be impaired relative to age-matched controls only on the higher-level pattern masking task. On the peripheral masking task, Alzheimer patients were no worse than their age-matched controls, although both age groups had higher critical SOAs than the young control subjects. As we discussed, it is not clear whether the deficits in the elderly are due to a deterioration of the ocular medium (pupils, lenses, cornea, humours) or to the slow neural degeneration of the geniculostriate system. Whatever the cause, it is consistent with the notion that homogeneous masking is a peripheral phenomenon.

On backward masking with a homogeneous flash, Alzheimer patients were no worse than their age-matched controls although both groups required more processing time than the young to escape the effects of the mask. As with spatial frequency contrast sensitivity, these masking functions varied with acuity suggesting that relatively peripheral factors determined performance. It is difficult to decide, on the basis of currently available evidence, whether these factors are extraneural, such as age-related changes in the ocular media, or neural, such as cell loss in the primary projection pathways in the geniculostriate system that is found to the same degree in normal elderly people as in Alzheimer patients (*see below*).

On pattern masking, however, Alzheimer patients differed significantly from their age-matched controls, who in turn differed from the young. Although it is known that some peripheral factors also influence performance on the pattern masking task under monocular presentation, there is sufficient evidence to indicate that additional higher-order central factors are involved. Walsh (1982), for example, found that in the normal elderly, performances on the two masking tasks do not correlate well with each other. As a more direct test, Byrd and Moscovitch (cited in Moscovitch, 1982) restricted participants in their masking study to those individuals whose acuity was sufficiently good for them to detect words exposed for 2 ms at normal intensity and contrast. As expected, these elderly individuals who took only a little longer to

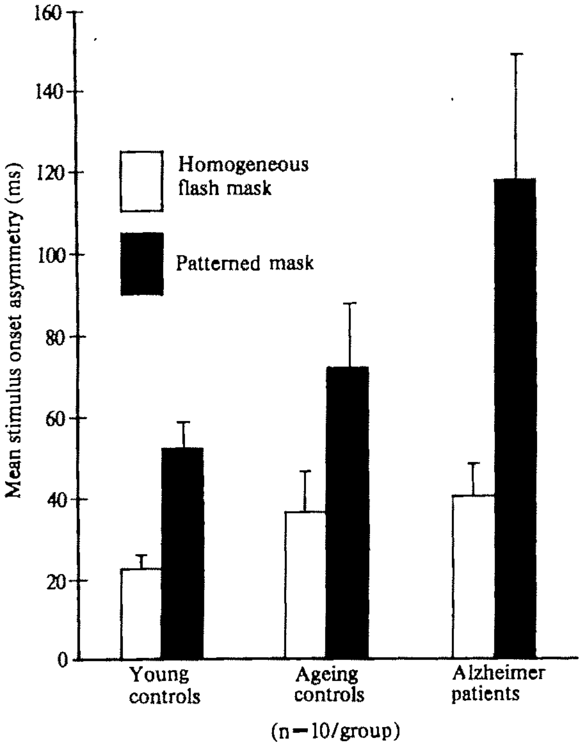

FIG. 2. The effects of normal ageing and Alzheimer's disease on visual masking performance. Mean stimulus onset asynchrony in ms when interstimulus interval is zero is compared for young, ageing and Alzheimer groups for homogeneous and pattern masking conditions. The error bars represent standard deviations.

escape the effects of the peripheral mask required much more time than the young to escape the effects of the central pattern mask, but these results parallel those between normal elderly and Alzheimer patients in our study.

That performance on backward pattern masking can differ among individuals with equivalent visual acuity and homogeneous masking functions reinforces the view that pattern masking is a higher-order central phenomenon that is not completely determined by peripheral factors. From a functional point of view, backward masking with a homogeneous unpatterned stimulus affects target perception by interfering with the extraction of physical features of the target such as its brightness, contrast and contour. Changing the brightness and contrast of the target or mask will have a profound effect on homogeneous masking functions (*see* Turvey, 1973; Coltheart, 1980, for review). It is easy to see, therefore, why performance on the masking task will vary with acuity or with any alterations in the ocular media that produce changes in the physical quality of the stimulus. Backward pattern masking, on the other hand, is believed to operate by interrupting the action of a central processor that integrates these physical features into relational or categorical information. Consequently, once it occurs centrally, central pattern masking is relatively immune to changes in the physical features of the target. What is critical is the total time the central processor has to integrate these features into a relational percept. The results from our study suggest that the central processor, which slows down somewhat with age as others have observed (Birren, 1965), is slowed even further by the degenerative effects of Alzheimer's disease. As a result, it needs more time to complete its task and is, therefore, susceptible to the effects of the mask for longer intervals.

This framework can be used to explain the unexpected finding that target identification, even in the absence of any mask, paralleled the performance of our three goups in the pattern masking study. Clearly, to identify a letter, a central processor is needed to integrate physical features into a meaningful percept. Peripheral factors are responsible for the degraded or delayed input of these features to the central processor. In addition, the termination of the target itself produces a signal that may act as a pattern mask to interrupt the central processor (Breitmeyer and Ganz, 1976). Lastly, it is conceivable that the deterioration of central areas outside the visual system that are concerned with verbal processes may also have contributed to the increased threshold of letter identification in old people and Alzheimer patients.

EXPERIMENT 3. SPATIAL EXTENT OF BACKWARD PATTERN MASKING

The focus of the study thus far has been on temporal factors affecting performance on masking tasks. Spatial factors, however, are also important. It is known, for example, that for the pattern mask to be effective, its contours must lie in close spatial proximity to the target. If there is loss of resolving power with age, as our findings on acuity and contrast sensitivity suggest, the spatial extent over which pattern masking is effective should increase. By determining whether this increase is retarded or accentuated by Alzheimer's neuropathology, information can be gained about its effects on the spatial organization of neural networks.

Subjects

Except for two Alzheimer patients who were not available, all the subjects who participated in the previous masking studies took part in the experiment.

Procedure

The target duration was set at the value at which each subject reached criterion performance of four consecutive correct identifications of the target with a flash mask at zero ISI. The pattern mask was then superimposed directly over the target stimuli and presented at zero ISI. After each identification error the patterned mask moved to the left by 0.125 deg. The lateral displacement necessary to return to criterion performance was thus determined. At this displacement the pattern mask would be no more effective than the flash mask.

Results and Comment

As predicted, for the pattern masking stimulus array to be no more effective than a featureless homogeneous flash, the ageing control group required an average displacement of 1.54 deg which was consistently greater than the 0.91 deg displacement required by the young (ANOVA, $F(1,19) = 4.56$, $P < 0.05$). This statistical significance is lost after adjustments for the covariate of visual acuity (ANOVA, $F(1,19) = 0.27$, $P < 0.5$). No differences were seen between normal ageing and Alzheimer's disease groups who required an average displacement of 1.25 deg (ANOVA, $F(1,20)$, 0.54, $P < 0.5$).

In general it appears that increases in the spatial extent of the metacontrast masking effect coincides with the decline in visual acuity which accompanies advancing age. No further increases are seen as a result of the neuropathology of Alzheimer's disease. If Alzheimer's neuropathology leads to functional neural loss, we might have predicted that the possibility of spatial interaction should have been reduced as functional neural networks shrink in size. This shrinkage might have overcome the increased spatial extent of interaction that occurs due to loss of resolving power with age. Although the spatial extent of metacontrast is smaller in Alzheimer patients than in the elderly, the differences were not significant. These results thus indicate that the spatial organization of neural networks mediating pattern masking is not as grossly affected as temporal organization by Alzheimer neuropathology, at least in the relatively early stages of the disease at which our patients were tested. This is not surprising in that the results also suggest that relatively peripheral factors, such as those related to acuity, influence the degree of spatial displacement over which a pattern mask is effective.

DISCUSSION

Impaired visual functions in Alzheimer patients are of two types—those which are mild and result from changes that normally accompany old age and those which are severe and are exacerbated by the neuropathological processes of dementia.

The first is correlated with loss of visual acuity and is of no greater severity than that found in intellectually normal aged individuals. Thus, visual acuity, spatial frequency contrast sensitivity, and susceptibility to homogeneous visual masking is equivalent in Alzheimer patients and age-matched controls, although both groups are impaired when compared with young individuals. The clear relationship between declining visual acuity and performance on the latter two tasks suggests that the deficits are relatively peripheral and associated with declining sensitivity to low-contrast, high spatial frequency targets in old age. This pattern of results is consistent with those most recently reported by Owsley (1982) and Sekuler and Owsley (1982). Much of the spatial luminosity information which is necessary for correct identification of sharp edged visual targets falls in the middle and upper spatial frequency range (Campbell *et al.*, 1971; Hood, 1973; Graham, 1981). If detection of these frequencies is slightly impaired, as it appears to be in the normal ageing adult, then performance deficits would be expected on tasks, such as backward masking with a homogeneous flash, that directly manipulate apparent contrast.

The second type of impairment, which is associated with higher-order, central visual processes, seems to be independent of visual acuity. Alzheimer patients needed twice the duration as normal aged people to reach the threshold of letter identification, although both groups were matched for age and visual acuity. Similarly, Alzheimer patients were much more susceptible to the effect of backward masking with a pattern. Both these tasks impose limits on the time available for the formation of a patterned relational percept. The sudden presentation of a contour, as in pattern masking, or the termination of an existing contour, as in letter identification threshold, is believed to disrupt ongoing central visual information processes (Turvey, 1973; Breitmeyer and Ganz, 1976). These results strongly suggest that the speed of central visual processes that normally slow down with age is reduced even further in Alzheimer's disease. Interestingly, only temporal aspects of backward masking are noticeably altered in the early stages of Alzheimer's disease. The spatial extent over which the mask is effective is equivalent in Alzheimer patients and aged controls, although both groups are susceptible to the mask over a larger area than young controls. These results are reminiscent of Wilson's (1967) finding that in areas of impaired vision, temporal summation is altered only by postgeniculate lesions, whereas spatial summation is affected equally by both pre- and postgeniculate lesions.

As we discussed earlier, it is difficult to determine the structural locus at which both types of impaired function arise. The high correlation between visual acuity and the impaired functions that Alzheimer patients share in type and severity with normal old people suggest that they may result from changes in the physical ocular media that accompany old age. The loss of retinal illumination and resolving power as a result of changes in the lens, in pupil size, and of the composition of the ocular humours could lead to the age-related changes in contrast sensitivity and acuity. It is equally possible, however, that this impairment is associated with neural factors such as cell loss in the primary visual pathways or even with loss of efficiency of existing neurons. The latter could account for the slowing of visual processes with age even for low-level tasks such as are measured by backward masking with a homogeneous mask (Walsh, 1982) and by the persistence of visual sensations after the stimulus has physically disappeared (DiLollo *et al.*, 1982; Kline *et al.*, 1982). At the moment, it is difficult to decide between the two alternatives. In any event, the evidence does suggest that the source of the impairment is relatively peripheral in that it is not likely to affect structures central to the primary visual pathways. With regard to Alzheimer's disease, it indicates that the degenerative processes spare these visual functions, at least in the early stages of the disease. Thus, although the primary visual cortex contains some Alzheimer's histopathology, such as abundant senile plaques but sparse neurofibrillary degeneration, the visual functions traditionally attributed to this area remain relatively preserved. Consistent with this view is the finding that metabolic functions as measured by PET scan are normal in the primary visual cortex in Alzheimer patients (Benson *et al.*, 1981).

In contrast, neurofibrillary degeneration is extensive and metabolic processes are abnormal in areas such as prestriate, posterior temporal and parietal cortex that are central to primary visual cortex. Functions related to form perception, such as patterned masking, that are thought to be mediated or dependent on input from these areas (Gross and Mishkin, 1977) are severely impaired even in the early stages of Alzheimer's disease. Because the spatial extent of masking is severely limited, even in Alzheimer patients, it suggests that masking effects are mediated by areas that still retain fine retinotopic organization. This does not exclude the possibility that areas involved with more abstract verbal processes also contribute to letter identification. Their deterioration, which is known to occur in Alzheimer's disease, can also contribute to deficits in letter identification in the absence of masking.

Although the results of our study are by no means conclusive, they attest to the viability of our working hypothesis that visual processes up to and including the striate cortex are normal in Alzheimer patients whereas those central to it are impaired. Encouraged by these results, we have recently begun to examine such functions as colour vision and stereoscopic depth perception which require intact extrastriate areas for normal performance (Zeki, 1973, 1978; Pearlman *et al.*, 1979; Ratcliff and Cowey, 1981). Preliminary evidence indicates that stereoscopic depth perception (G. R. Schlotterer, unpublished observation) and colour vision (Moscovitch, 1982) are impaired in Alzheimer patients whereas brightness discrimination, which seems not to be as dependent on these areas, is relatively normal.

Whatever the ultimate fate of our working hypothesis, it is clear from our findings that perceptual processes merit further investigation in Alzheimer patients. Because so much is already known about the neural organization of perceptual systems, such research may not only provide clues about the way Alzheimer pathology affects normal function but also about the relation between neural structure and complex perceptual processes in normal people.

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ADDENDUM

After this paper was accepted for publication, the authors were informed of a poster presentation at the Association for Research in Vision and Ophthalmology in 1983 by M. J. Nissen, S. Corkin, J. Growdon, S. Wray and J. Bauer entitled 'Spatial contrast sensitivity in Alzheimer's disease'. They reported that an unselected group of Alzheimer patients showed spatial frequency contrast sensitivity deficits at all frequencies between 0.5 and 8.0 c/deg. Because their testing procedure was similar to ours, it is not clear what caused the discrepancy between our results and theirs. One possibility is that all our patients had Snellen acuity equivalent to age-matched controls whereas theirs may not have. Since they do not report Snellen acuity in their poster, it is difficult to ascertain whether this is a critical variable. For the moment we still wish to conclude that most Alzheimer patients with normal Snellen acuity also have normal contrast sensitivity functions.

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EDITOR'S NOTE

LOCALIZATION OF FUNCTION IN THE CEREBRAL CORTEX

A meeting on this topic, sponsored by the Guarantors of *Brain*, was held in Hertford College, Oxford, on August 4 and 5, 1981. Its purpose was to commemorate the centenary of the International Medical Congress held in London in 1881, during which, on August 4, the famous confrontation between David Ferrier and F. Goltz took place. The following report by C. G. Phillips, S. Zeki and H. B. Barlow describes the events of one hundred years ago that inspired the 1981 meeting, summarizes the discussions that took place, and ends by attempting to integrate, in a speculative way, current concepts of cortical function.

LOCALIZATION OF FUNCTION IN THE CEREBRAL CORTEX

PAST, PRESENT AND FUTURE

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SUMMARY

At a famous meeting of the International Medical Congress held in London on August 4, 1881 Goltz of Strassburg (as it was then spelt) confronted Ferrier of London on the subject of the localization of function in the cerebral cortex. In the first part of this paper the events of that meeting are recalled. Goltz was reluctant to accept the idea of localization because of the restitution of function after injury to the cortex, and because of the general rather than specific residual disabilities of his lesioned dogs. On the other hand, Ferrier's monkeys with cortical lesions demonstrated convincingly that local lesions can produce loss of specific functions.

One hundred years later a meeting was held in Oxford on the same topic, and the discussions that took place are summarized in the second part of this paper. No-one doubted the doctrine of localization, namely that different parts of the cerebral cortex normally perform different specialized roles. However, there was no unanimity about how to separate or count the number of different parts of the cortex, nor about the nature of the specialized roles of the parts, nor about any common characteristics of the functions of different parts. In other words, though localization was agreed upon, precisely what the functions are that are localized remained obscure.

The third section of this paper advances some speculations on this point. Is a theory of cortical function that would encompass the diverse roles of different parts perhaps within sight, which might even explain the plasticity that must underlie the restitution of function that so impressed Goltz one hundred years ago?

ONE HUNDRED YEARS AGO

The *Discussion on the Localisation of Function in the Cortex Cerebri* that took place at a meeting of the International Medical Congress on the morning of August 4, 1881 marks a turning point in our knowledge of this subject. The meeting took place in London, Michael Foster was in the chair, and Goltz (1881*a*) was the opening speaker. He accepted the results of electrical stimulation of dog and monkey cortex (Fritsch and Hitzig, 1870; Ferrier, 1873; Ferrier, 1875), while noting the absence of any motor response to stimulation of wide areas; but he considered the excitation method inconclusive in that the movements elicited by it might have originated in afferent or efferent pathways as well as in centres, and because the stimulating currents might have spread physically through the cortex into centres lying deep to it. Ablation experiments were therefore essential to complement the results obtained by excitation, and were, indeed, preferable. The apparently complementary results of the two methods, together with some support from pathology, had led to a general acceptance of the doctrine of localization by textbook writers and by the medical public—in spite of wide differences between the functions assigned to the same areas by Ferrier and by Munk. The new doctrine had been found tempting. A fruit, also, may look tempting and yet be worm-eaten at the core. And the worm-eaten core of the doctrine of localization was the restitution of function after ablation.

Goltz's experiments on dogs had found no regrowth of the cortical areas that had been ablated, and had shown that the surviving parts of the brain actually shrink after damage to the cerebrum. If there is no regrowth, he argued, then restitution of function must be by the activity of surviving areas of the cortex. But according to the theory of localization, every area has its unique function. Then after restitution, one or more areas must have more than one function. And if after the operation, why not also before? Goltz ridiculed the notion he ascribed to Munk, that each centre is surrounded by virgin cortex which becomes active only after damage to the centre: that so much cortex is there merely to guard against the risk of mutilation.

Goltz's ablations were large and bilateral and were made, in several stages, by directing a jet of water onto the exposed cortex. He ascribed his successful results to the long survival of his dogs. Permanent deficits were limited to the higher psychic functions, especially intelligence. So Flourens had been wrong in supposing that any surviving remnant of cortex could fulfil all functions. Ferrier had been wrong in ascribing intelligence to the frontal lobes, since lesions which spared these lobes disturbed intelligence severely. Impairment of motor performance contralateral to unilateral lesions recovered completely in a few weeks. Hitzig and Ferrier had been correct in noting blindness of the contralateral eye [*sic*] but this also recovered completely. In vision the permanent deficit was what Munk had called psychic blindness (*Seelenblindheit*), but which Goltz preferred to call cerebral weakness of vision (*Hirnsehschwäche*). The dogs avoided obstacles but did not recognize food and were not frightened by strangers or threats. Similarly with other senses: they were not deaf, for they started when a whip was cracked, but did not run away, and did not bark when other dogs barked. Nor were they deprived of smell and taste, for they would eat food when it was given to them—though they would accept dog flesh, from which normal dogs recoil in disgust, and would inhale tobacco smoke or chloroform vapour. Again, they reacted to strong stimulation of the skin, but would stand still in cold water and did not orientate themselves to a touch.

The water-jet experiments had not been specifically directed to the question of localization, and Goltz had made more precise lesions with a small spiral saw in a drilling machine. Bilateral ablations of the anterior quadrant, including the excitable zones, caused no permanent paralysis, in spite of the destruction of Ferrier's psychomotor centres, Munk's sphere of touch, and Hitzig's muscle sense, even if the lesion was several centimeters deep and extended into the lateral ventricle and striatum. Such a dog would replace a limb which had been displaced into an unnatural position, and could even 'give a paw' contralateral to a unilateral lesion. After bilateral parietal lesions, however, the dogs were decidedly more awkward in their movements, slipping on a slippery floor and unable to hold a bone with a forepaw when gnawing it. Bilateral posterior lesions injured a large area of cortex and the animals were correspondingly more stupid; they were not blind for they avoided obstacles: they had visual sense without visual areas. Even in cases of very large, deep bilateral lesions, causing extreme stupidity, there was no absolute loss of vision, hearing, taste, smell, or touch, and no paralysis. In one such case, the brain weighed only 13 g (normal, 90 g).

Goltz concluded that the cortex is the organ of the higher psychic functions (*höheren Seelentätigkeiten*). Intelligence is permanently impaired by large lesions, but no local lesion can cause permanent paralysis of any muscle or permanent loss of any sensation.

Ferrier (1881*a*) said that if he could not agree with Professor Goltz it was not because he disputed his facts. 'These, from Professor Goltz's character as a trustworthy observer, I should be prepared to accept without further verification. But, I reject his conclusions.' The conflict was between results obtained in different species. All of these had to be accommodated in any general theory. The hypothesis [*sic*] of localization accommodated the results in monkeys and dogs, whereas Goltz's hypothesis was irreconcilable with the results in monkeys.

Goltz differed from Flourens in admitting that the posterior part of the brain is more concerned with vision, the anterior part more with motor power than sensation. This was 'a very significant concession, and is practically admitting the doctrine of localization, and I am hopeful that Professor Goltz may yet see his way to admitting it in a more thorough-going manner'.

Goltz had assumed that restitution of function in his dogs had been due to areas of cortex which remained intact. To prove this, the whole of the cortex would have had to be ablated and all faculties thereby annihilated. Ferrier turned to the facts of comparative anatomy and physiology. In frogs, pigeons, rabbits and others 'low in the animal scale', even complete extirpation of the whole cerebral hemispheres had comparatively little effect on the powers of locomotion and reaction to sensory stimulation. 'Professor Goltz has now shown us how much even dogs can do when their cerebral hemispheres have been extensively destroyed.' Higher up the animal scale—in monkey and man—paralysis is permanent.

Ferrier's main concern, however, was not so much to criticize and explain Goltz's results as to bring forward the results of new experiments on monkeys. In his earlier experiments, survival time had had to be kept short in order to avoid errors of localization due to secondary extension of the lesions by infection. Though these experiments were of less value for the study of restitution, they were valid as evidence of localization. In the past two years, there had been opportunities to observe monkeys operated on by his colleague Gerald F. Yeo, Professor of

Physiology at King's College, in the course of his investigations into the application of the principles of antiseptic surgery to the brain. In these animals, the lesions were made by cautery, and were accurately confined to the areas whose functions were to be investigated; and lack of secondary extension was verified microscopically after longer periods of survival.

Ferrier reported experiments on five monkeys. In the first, a lesion 1.0 cm in diameter, pre- and postcentral (for Ferrier's excitation maps included the postcentral gyrus), caused monoplegia of the opposite arm without other deficit. Tactile sensibility of the hand was 'most acute' (but was tested by 'the slightest touch with a heated point'). This animal survived two months before succumbing to the cold winter. The second exhibited monoplegia of the opposite leg and was kept for eight months, when the lesion and degeneration descending from it were defined post-mortem. The third, hemiplegic, monkey was still alive seven months after the operation, and showed no loss of tactile sensibility (to the heated point?) 'as frequently found in clinical practice', and no other deficit. The fourth showed blindness, and no other deficit, after bilateral ablation of occipital lobes and angular gyri. After some months it avoided obstacles. It, too, died in the winter cold. In the fifth monkey, which was still alive, bilateral temporosphenoidal lesions caused deafness but no other deficit. Ferrier concluded that 'Professor Goltz's hypothesis is erroneous, and that such facts are explicable only on the theory [*sic*] of a distinct localization of faculties in definite cortical regions'.

In the afternoon, members of the Section were invited to visit the Laboratory at King's College, London to examine the dog which had made the journey with Goltz from Strassburg, and two of the monkeys of Ferrier and Yeo.

Goltz's dog (1881*b*) had had five operations between November 1880 and May 1881. When its box was opened it reared up on its hindlimbs. It ran around actively, wagging its tail continuously. The hindlimbs slipped on a slippery floor. It avoided obstacles, but appeared to lack visual fixation. It did not withdraw from a candle held close to its face. (Goltz had mentioned in the morning that it had even licked the face of a spitting cat.) A gentleman lit a cigar and blew smoke in its face, from which it did not withdraw, but only turned its head when much smoke was blown. It was not deaf, for it moved its head when a whip was cracked, but did not crawl away. That the skin was everywhere sensitive was demonstrated by squeaking and struggling when an aesthesiometer specially constructed by Ewald reached a threshold pressure. Goltz concluded that no sensory function was lost and that there was no paralysis. The animal's general stupidity was evident in its failure to respond to threatening or friendly gestures and to escape from a fence lower than the height of the box from which it could always climb out. The dog would be killed with chloroform so that members could see for themselves the enormous lesion.

Ferrier (1881*b*) then exhibited two of the monkeys he had described that morning. The first was the hemiplegic animal in which, after seven months, movements of the contralateral leg were 'greatly impaired' and the arm was 'quite powerless . . . flexed at the elbow, the thumb bent on the palm, and the fingers semiflexed. Charcot was heard (by Sir Charles Ballance) to remark 'It is a patient!' The animal was stated to be in every other respect normal (but no examination of somaesthetic function was demonstrated). The second was the monkey with bilateral superior temporo-sphenoidal lesions of ten weeks' duration. It showed no sign of paralysis or blindness. 'While the two monkeys were on the floor together before the audience, Dr Ferrier snapped a percussion cap in their immediate proximity, whereupon the hemiplegic monkey started with the most lively signs of surprise, whereas the other exhibited not the slightest indication whatever of hearing. This experiment was repeated several times with the same result.'

Yeo (1881), who had performed the operations, said that his special interest had been in the surgical problems involved in operations on the brain, and that he had embarked on them 'with distinct misgivings as to the existence of local cortical centres, in Ferrier's sense'. He thought that the negative results in dogs could not argue against the positive results in monkeys, which 'seem to curtail in an absolute manner the very extensive generalizations Professor Goltz wishes to draw from his experiments'. Yeo thought that the field of vision of Goltz's dog was restricted or his sight deficient, because he suddenly stopped before an object, or bumped the right side of his head (Goltz had said the left side of his body). The dog seemed to know his friends, because he had learned in three or four days to recognize the person who fed him in London. If he did not react to Goltz's threats, this might have been simply because he had learned that they were never carried out. If his gait was unnatural, this was not from want of intellectual power but due to distinct loss of power over his hind legs. 'Besides expressing how much I have learned from my learned friend Professor Goltz, I candidly admit that, should the entire of the so-called motor centres prove to be destroyed in this case, he has succeeded in completely changing my views on the question of cerebral localization.' Yeo expected that much of this dog's cerebral cortex would be found intact. Having seen the monkeys' circumscribed lesions whose accuracy had been made possible only by the aseptic [*sic*] method, 'I feel sure that Professor Goltz will modify his opinion as to the 'utter folly' of the view that special parts of the brain are peculiarly associated with certain functional departments, and, though I am far from endorsing the edicts of Munk, or accepting, without reservation, the views of Ferrier, I venture to hope that our friend from Strassburg will no longer think that the observations which describe any persistent functional disturbance, as a result of a local lesion of the brain cortex, are *einfach falsch*.'

The dog and the hemiparetic monkey were then killed under chloroform. The brains were removed with the assistance of Professor Purser, Dr Gaskell and Mr Langley and were shown at the next meeting of the Section of Physiology. The frontal lobes of the dog were intact, and part of the so-called motor areas remained on the left. Much of the temporal lobes remained intact, together with strips of parasagittal and occipital cortex on both sides. In spite of the more extensive damage to the right hemisphere, Goltz insisted that there had been no asymmetrical deficiency during life, and no paralysis. The monkey showed a well circumscribed but very extensive lesion, post- as well as precentral. Drawings of both brains were published in the Transactions, which appeared before the end of the year.

The Council thought that, in attempting to come to a conclusion on the somewhat conflicting results, it would be very valuable to obtain exact knowledge of the amount of grey matter destroyed in each case. Having learned that 'the gentlemen to whom the animals belonged most cordially agreed to this arrangement', Foster proposed that the brains be entrusted to a Committee nominated by Council: Drs Gowers, Klein and Schäfer and Mr J. N. Langley. 'The foregoing suggestions were unanimously carried.' Preliminary reports by Klein (1881) and Langley (1881) on the dog, and by Schäfer (1881) on the monkey, were also included in the Transactions. Their full reports were published later (Langley, 1883; Klein, 1883; Schäfer, 1883).

Envoi

The afternoon at King's College had its sequel in November at Bow Street Magistrate's Court. Ferrier had to answer a summons applied for by three barristers for violation of the Vivisection Act [*sic*] of 1876. The Magistrate dismissed the summons. The Proceedings were reported verbatim in the *British Medical Journal* (1881, **2**, 836–842).

Langley had Sherrington's collaboration in his examination of the right hemisphere of the dog. Langley and Sherrington (1884*a*) demonstrated sections to the Physiological Society, and a full paper by Langley and Sherrington (1884*b*) was published later in that year.

Goltz continued to make ever-wider ablations in dogs and published the results of complete removal of the forebrain (1892). The dog's behaviour was similar to that of the dogs of 1881. Serial sections of the brain had been cut in Edinger's laboratory at Frankfurt; these were given to Gordon Holmes who described and illustrated them in his paper on 'The nervous system of the dog without a forebrain' (1901). Sherrington, who visited Goltz's laboratory in the winter of 1884–5, was also given a brain and spinal cord which he also described (1885). As time went on, Goltz (1888) convinced himself (always on dogs) that amputations of different lobes had different consequences, but he considered the assumption of small circumscribed centres more nonsensical than ever.

PRESENT PROBLEMS

The centenary meeting took place in Hertford College, Oxford on August 4 and 5, 1981. The participants are listed in the Appendix. It was organized in four sessions of three hours each at which the chairmen tried to encourage general discussion on such topics as: are there any principles of cortical organization common to all the sensory areas of the cortex? What is the significance of topographic and nontopographic maps? What functions are represented in cortex, especially motor cortex? Is there a basic structural and functional uniformity in the organization of the cortex? In the hope of providing a starting point and some common ground for the discussion, reprints of papers by some of the participants had been precirculated (Barlow, 1981; Iwamura *et al.*, 1981; MacKay, 1978; Phillips, 1981; Zeki, 1981).

In contrast to the meeting one hundred years earlier there were no dramatic confrontations, nor was there any single topic that dominated the meeting. Instead the general mood might be described as that of a group who appreciated the fiendish complexity of the organ they were studying and of the tasks it performs, and were consequently wary of accepting generalizations that would probably appear simplistic in a few years' time. Much experimental material was briefly introduced and discussed, but it is probably fair to say that most enthusiasm and optimism was shown for the potentialities of modern anatomical methods. Though the detail that these methods reveal is at present almost totally incomprehensible, they do seem capable of providing information about the types of cells, their numbers, and their patterns of interconnection, upon which our future understanding of how the cortex really works must be based.

The discussions at the meeting were, to say the least, somewhat inconclusive, but during its course a number of suggestions were made that may possibly be welded together into a general theory of the cerebral cortex, and we shall expose ourselves to possible ridicule by attempting to do this in the final section of this paper. At this point it is worth mentioning these ideas so that the reader can see how they arose in the discussions. The first is the idea that there is a single basic operation performed in all parts of the cortex, and that this may be the detection of associations, or covariation, or 'suspicious coincidences', among the inputs to each particular small region of cortex. It can be shown that the performance of this task is much simplified if the nerve cells communicating with each other in the cortex adopt a uniform 'cortical language', or system of conventions. This in turn leads to an appreciation of the importance of the redistributive role of cortex, for it seems that the organized redistribution of information, perhaps according to nontopographic principles, may be what makes it possible for one small part of cortex to receive the inputs among which associations or coincidences of crucial importance to an animal's success or survival can be detected. Another set of ideas came from discussions about the changes in mapping that occur when sensory input is changed, and the possible role of the inputs to layer 1 as a 'state control' managing such changes. We shall return to these different strands of thought in our attempt to formulate a preliminary general model of the cortex, but first an account of the free ranging discussions will be given.

Lessons from Lesions

A hundred years ago, when Goltz and Ferrier were arguing about the cerebral localization of function, cortical cytoarchitectonics was in its infancy. Neither Campbell (1905), Brodmann (1905), nor von Economo and Koskinas (1925) had charted the cortex, studies of the anatomical connections of the brain were virtually unknown, and microelectrode physiology was a thing of the future. The arguments were thus based on what appeared to the scientists of that time as the best evidence available, namely, whether lesions in particular parts of the cortex affected particular functions. In today's terms, the lesions were very crude, often spanning (as in Ferrier's studies) what we now consider to be separate cortical areas. Equally, the questions asked appear to us to be simplistic. Our predecessors asked whether vision, or general sensation, or motor function, was localized; and they did not probe in detail into the submodalities of vision or general sensibility or into different categories of movement or posture.

A hundred years on, today, there is a wealth of information on the cerebral cortex. Sophisticated anatomical and electrophysiological techniques have apparently resolved all doubts, if such there were, that different parts of the cortex are indeed specialized. No one would seriously question the proposition that the visual and somatosensory areas, or the auditory and motor areas, execute radically different functions. But paradoxically, in spite of the wealth of information on the cortex now available to us, some of the most suggestive evidence for functional localization still comes from the same kind of study that so impressed scientists of a century ago. Thus, the description by Zihl *et al.* (1983), related at the meeting by Fries, of a patient with a bilateral symmetrical prestriate lesion demonstrated by CT scan, who was unable to detect motion although perfectly able to read, see forms, colours and depth, was perhaps one of the most convincing accounts in favour of functional localization. It was reminiscent of the recent work of Pearlman *et al.* (1979) who described a patient with a posterior cerebral lesion. This patient, like that of Mollon *et al.* (1980), was massively impaired in his ability to discriminate colours, although his perception of depths and movements, as well as his reading ability, was unimpaired.

If animal experiments could reproduce these results derived from human patients, then much that seems ambiguous when electrophysiological and anatomical studies are compared with behavioural ones would be resolved. Unfortunately, such evidence is not easy to come by. Cowey reported (Collin and Cowey, 1980) that lesions in the motion area (V5) of the superior temporal sulcus in monkeys, an area in which directionàlly selective cells predominate (Zeki, 1974), results in no observable defect. By contrast, lesions in visual cortex result in a fairly profound increase in threshold for disparity, though this may simply reflect damage to the foveal areas where acuity is high (Cowey and Porter, 1979). Equally, large lesions of the striate cortex, known to have a preponderance of orientation selective cells (Hubel and Wiesel, 1962, 1977), lead to only a slight rise in threshold for discriminating different orientations (Pasik and Pasik, 1980). At first this seems to imply that we are not able to infer functions of an area from our physiological studies, perhaps because several different areas cooperate in a perceptive task and we are therefore naïve in supposing that we can restrict our lesion to a single functional area and see a single functional defect. But this disappointing conclusion may result from preconceptions about function that lead to asking the wrong questions and performing the wrong tests. Thus Berkley and Sprague (1979) found only small deficits in grating acuity of striate-lesioned cats, and even orientation discrimination was only decreased by a factor of about 2. On the other hand vernier acuity was practically abolished, a result that fits well with the idea that the striate cortex is involved in tasks requiring high positional accuracy (Barlow, 1979, 1981). Clearly we must be a good deal more exigent in our definition of function, and this lesson was re-emphasized in the discussions on multiple maps (*see below*).

What Constitutes a Cortical Area?

It is not surprising to find that our definition of a cortical area is no longer quite as simple as the one conceived a hundred years ago, and at the meeting various problems were raised, but no agreement was reached. Zeki considered the best known example of an area, namely, area 17 of monkey cortex. Everything about it suggests that it is a single area. It has a uniform cytoarchitecture, a uniform distribution of ocular dominance columns and a uniform input from the lateral geniculate nucleus (LGN). As well, it has a complete and topographic representation of the retina. Yet in other properties it is nonuniform and if these were emphasized it might be concluded that it is not a single area. Zeki reported that his results, as well as the earlier ones of Poggio *et al.* (1975), show that the distribution of so-called 'colour coded' cells is not the same all over area 17. Instead, the frequency of such cells reaches about 40 per cent in the representation of the central 2 deg, and there is a rapid decline at increasing eccentricities, so that at an eccentricity of 20 deg no more than 2 per cent of cells are 'colour coded' (Zeki, 1983). In this context, he noted that the percentage of 'colour coded' cells in the V4 complex has been compared misleadingly to the percentage of such cells in foveal V1 (central 2 deg). The comparison is misleading because, unlike V1, only the central 20 to 30 deg of the retina is represented in the V4 complex and the receptive fields of the cells in the latter are about four times larger than in the former. Moreover, unlike V1, there is no strict topography in the V4 complex, with the consequence that in any single penetration, even a perpendicular one, receptive fields can cover the central 10 to 15 deg, or even more. It follows that to make an adequate comparison of the percentages of 'colour coded' cells, equivalent eccentricities in the two areas must be sampled. Indeed, if foveal VI and the V4 complex were compared, it would be found that the percentage of 'colour coded' cells is more or less similar. However, if the proportion of such cells within the central 10 to 30 deg in V1 and in the V4 complex were compared, a substantial difference would be evident (Zeki, 1982*a*, *b*). This in fact raises the general problem that the distribution of any given category of cell is not necessarily uniform across the whole of an area. For example, the distribution of orientation selective cells varies with eccentricity in V1 and the V4 complex, but in opposite directions (Zeki, 1982*a*). Similarly the distribution of 'colour-coded' cells is eccentricity dependent in V1 and follows other, and unknown rules, in the V4 complex (Zeki, 1975, 1983). Hence the information obtained by studying any given small region of an area, such as V1, is not necessarily true for the whole area. Foveal VI, for example, is substantially different from more peripheral V1.

Although these differences may be nothing more than a result of the topographic projection of a nonuniform surface (the retina) on to a highly uniform one (the striate cortex), the fact remains that just such functional and anatomical differences have been used to distinguish other areas from each other. How should this difficulty, which mainly arises from improved anatomical and physiological techniques, be overcome? Crick suggested that while features across an area may not be uniform, the changes may be gradual rather than abrupt. Perhaps, then, abrupt changes should be sought as a means of defining a boundary. But it is essential to look for abrupt changes not in just one feature, but in several features simultaneously. If we concentrated on a single feature, we might well be tempted to consider the peripheral monocular and binocular parts of area 17 to constitute two areas!

Mountcastle amplified this by saying that gradients, and even sudden changes, do occur within an area, but at the borders there are abrupt changes in all layers simultaneously, even when there are no corresponding abrupt changes in the afferents and efferents. One example is the sudden change in receptive field size and the heavy emphasis on binocularity from V1 to V2 across the cytoarchitectonic boundary. Another is the sudden change in receptive field size and the heavy emphasis on directional selectivity on moving into V5 (Zeki 1974, 1981). Both these changes affect all layers simultaneously.

Nor were the difficulties of defining an area restricted to visual cortex. Merzenich related how the input to the different areas of the auditory cortex in cat is in parallel, there being no 'primary' auditory cortex (Merzenich, 1981). A1 is subdivided into bands of excitatory-excitatory and excitatory-inhibitory interactions between input from the two ears. Tangential penetrations show discontinuous steps in best frequencies. Is A1 therefore a functional area or, on the arguments applied to area 17, should each of the local substructural units be considered a distinct cortical area? According to von Economo the cytoarchitecture of A1 is not at all uniform. Yet these excitatory-inhibitory and excitatory-excitatory bands might merely reflect the nonhomogeneity of the commissural connections of A1, which should still be considered a single area, especially since an abrupt change occurs in both the tuning curves of cell responses and in the cytoarchitecture at the border of A2.

The discussion could be summarized by saying that the old cytoarchitectonic boundaries do not necessarily mark the only changes in the cortex, but they are still very useful guides to important changes of function.

Are Maps Outmoded?

If there was no unanimity of views on what constitutes an area, this was at least in part a consequence of changing concepts about the representation of function within cortical areas. One change is that the old argument about motor cortex has spread to other cortical areas. This argument revolved around whether the motor area is made up of dense, quasi-insulated projections to the motoneurons of individual muscles, these being somehow accessible to the Will, or whether the projections are overlapping. In the latter event, the significant organization, as Hughlings Jackson originally maintained, would be in terms of 'sensorimotor processes representing movements', that is, frequently used combinations and sequences of muscular activation, subject to control by the 'highest level' of the brain. The first hypothesis has now been falsified: it is firmly established that the projections overlap widely, and that single corticospinal axons branch to supply motoneurons of more than one muscle (Phillips, 1981). Recent work on monkeys reported by Lemon (1981*a*, *b*) supports the second hypothesis. He found that some neurons which sent their axons into the pyramidal tract discharged when the monkey was picking up seeds with its thumb and index fingers, but not when it grasped a ball with all five digits, although many muscles would have been common to both performances. Some neurons which discharged in relation to precision-gripping by thumb and index did so only when the wrist was in a particular orientation. The types of pattern selectivity discovered in cerebral cortex by Hubel and Wiesel point in the same general direction. Moving, orientated, lines and edges are frequently occurring combinations and sequences of activation of sensory afferents; they might be considered to be analogous to the most stereotyped and frequently used combinations and sequences of muscle activation required for a movement.

The demonstration by Mountcastle and his colleagues (Mountcastle, 1957; Powell and Mountcastle, 1959) of discrete groupings of cells in somatosensory cortex responding to particular sensory modalities introduced another new strand of thought. The participants at this meeting were thus searching for more sophisticated ideas about representation. They were not asking how the retina is projected onto the visual cortex, but how motion, form, or colour information may be organized there; not how the sensory surface may be mapped in the somatosensory cortex, but how different modalities of sensation are organized; not for yet more detailed mapping of connectivity between motor cortex and subcortical levels, but how the known connections are engaged in the combination and sequencing of excitation and inhibition of muscles in motor acts.

Iwamura (Iwamura *et al.*, 1981) reported recording from the somatosensory cortex in the awake behaving monkey, and finding that the representation of the fingers was neither orderly nor uniform. Of interest was his finding that neurons which were suspected to have restricted receptive fields from recordings in the anaesthetized monkey turned out to respond optimally only when the animal grasped, for example, a horizontal bar and thus involved several joints simultaneously. By contrast, Merzenich's results, also on monkey (Merzenich *et al.*, 1978, indicated a continuous representation of the hand in layer IV of area 3b; the representation of the digits was continuous, not separated by that of other parts of the hand. His result indicated that the mapping in the somatosensory cortex was constant over long periods in any single animal, but that there were differences between animals. In addition, there are gaps in the skin surface representation within area 1 and area 3b, and the gaps within the two areas are themselves different.

Other examples of discontinuities were reported. Among these are the gaps in the map such that the receptive fields of contiguous cells in the motion area (V5) may represent noncontiguous retinal positions, there being often striking jumps from the receptive field of one cell to that of the next (Zeki, 1980*a*, 1981). Zeki suggested that it may be misguided to consider such representations as 'disorderly' or 'chaotic' for they are such only in terms of a fixed anatomical structure, the retina, and it is only if it is insisted that the retina must be mapped on to such areas that the representation would appear chaotic. As Mountcastle reported, the receptive field of a cell in area 7 may include the entire visual field, perhaps sparing the area centralis, with marked specializations within the receptive field (Motter and Mountcastle, 1981; Yin and Mountcastle, 1977; Zeki, 1980*a*). To think of these maps as maps of the retina continues a rigidity of thinking inherited from the past.

Perhaps a more powerful approach is to ask how function, rather than position, is mapped in the cortex. In this form the question may even be asked of areas which years of research have shown to have a precise representation of the body surface, as in V1. Daniel and Whitteridge (1961) reported that V1 has a distorted representation of the retina due to the disproportionately large representation of the fovea. One reason for maintaining the topology of the map is that eye movements may require geometric mapping. This may be occurring in the pontine nuclei (gaze centres) to which the region of the central representation in V1 has little projection, but which receives a heavy projection from the representation of peripheral V1 (Fries, 1981).

Concepts of mapping and representation of visual space are largely derived from electrophysiological studies in which the receptive fields of single cells or groups of cells are plotted. Is this approach suitable when seeking to understand the higher functions of the cerebral cortex? Mountcastle suggested that the receptive field concept is not appropriate in 'association' cortex because the complex abstraction of a peripheral event is not describable in such terms (Mountcastle *et al.*, 1975; Mountcastle, 1976). The task here is to determine the type of behaviour that is related to the optimum discharge of cells. Nor should it be supposed that a single type of function necessarily resides in a single area of the cortex—that would be modern phrenology.

Nevertheless the possibility that there may be a relatively simple correspondence between the activity of cortical neurons and perceived sensation has been argued quite recently (Barlow, 1972), and this type of approach encourages advancing beyond the kind of question that is asked in the framework of conventional electrophysiology and seeking correlations between neural events and subjective experience. Colour vision provides one example: Zeki proposed that the so-called 'colour-coded' cells of V1 do not respond to specific colours at all, but only to the presence of sufficient amounts of their preferred wavelength in the light reaching the eye (Zeki, 1982*a*, *b*). This information is then used by the cells of V4 to assign colours to surfaces, and the pattern of activity in these cells corresponds simply with the subjectively seen colour (Zeki, 1980*b*). Crick thought that it might be useful to make a distinction between information represented implicitly and explicitly. For instance it could be suggested that colour is implicit in the response of cells in V1, but explicit in V4. That is to say, the responses of cells in V1 contain the information required to assign colour to a part of the visual field, but it is only in V4 that cells are found whose responses bear a simple relationship with perceived colour.

Another example of a possible simple correlate of cortical organization does not concern subjective experience but 'hyperacuity', the proven ability to assign a position to a marker in the visual field with very high precision, even when it is moving (Westheimer and McKee, 1975). This precision corresponds to an angle much smaller than the separation of foveal receptors, and Barlow (1979, 1981) has suggested that the very large number of granule cells in layer IV of the striate cortex might give a finer 'grain' than that of receptors in the retina. The work of Berkley and Sprague (1979), already cited, on vernier acuity in cats, certainly supports the idea that V1 is necessary for tasks demanding high positional accuracy.

Multiple Areas and Covariation

It might have surprised those thinking about functional localization one hundred years ago that there are, as we now know, a multiplicity of areas devoted to each modality. The question why this should be so is fundamental and was raised repeatedly at the meeting. The best known example is in the visual cortex, where many different visual areas have been demonstrated in the cat (Hubel and Wiesel, 1965*a*, 1969; Palmer *et al.*, 1978; Tusa *et al.*, 1978, 1979; Tusa and Palmer, 1980), in Rhesus (Zeki, 1974, 1978), and owl monkey (Baker *et al.*, 1981). One suggestion is that different visual areas, or groups of areas, are functionally specialized to execute or analyse different visual functions. But why need this be so and why cannot all functions be analysed in the same area? One possible answer (Barlow, 1981) is that information has to be reprojected and brought together, not only according to topographical position in the visual field, but also according to the value of some other variable of the stimulus, such as colour or direction of motion. As MacKay pointed out, there is potentially more information about a stimulus in an ensemble of cells than in any one of them, because of all the possible patterns of covariation among the cells. Thus the reason for having multiple sensory maps may be to make it possible to answer questions such as: What else happened when this happened? Clearly the types of covariation to be detected would differ from one function to another. For cells analysing colour, the question might be: What was the spectral composition of areas neighbouring to my receptive field when the spectral composition for my area was X? For cells detecting motion, the question might be: What else was moving in the same direction as the object in this receptive field? There are many different types of covariation. These may be purely sensory and may be unimodal or multimodal, or they may be purely motor or sensory-motor. Such an analysis of 'covariation' entails, as Barlow suggested, a redistribution of information, either within an area or between areas. It is precisely the execution of this apparently simple task that allows the cortex to detect the association of events in remote parts of the visual field, in different modalities, or the covariation of a sensory event and an item of motor action.

In this context Cowey emphasized several features (Cowey, 1979). First, cells which interact must be interconnected and this occurs most readily if the cells lie close together. Thus, if cells in the visual cortex related to adjacent parts of the retina are adjacent, the necessary interconnections can be shorter, which would be more economical of space and length of fibres. Also, they might be easier to specify genetically. He also suggested that if lateral inhibition is required to extract certain features from the stimulus (such as contour) this creates problems for interconnections unless cells extracting common features are kept together. This still raises the question of why, in some areas, discontinuities occur. The answer to this may lie in supposing that it is not necessarily geographical contiguity that matters. Functional contiguity may be significant. As an example, if it is desired to map motion in the field of view in the cortex, the precise topographical map that is evident in V1 would no longer be what is needed. Instead, it might be arranged that receptive fields with a common property, such as response to a particular direction of motion, reproject to the same small region of cortex so that covariation and association among them can be detected.

MacKay asked early in the meeting: What is V1 for? The answer that seemed to receive some support was: It detects *local* visual features, which are themselves associations of simpler stimuli. Barlow (1981), following Guzman (1968), called these 'linking features', and it is because they require information from adjacent parts of the visual field that a topographic map is required. The same question, applied to other visual areas, would receive the answer: They are for detecting the associated occurrences of the same linking feature (colour, direction of motion, disparity, or texture) in different regions of the visual field; they therefore do not require an accurate topographic map, but instead the organized representation of other variables of the stimulus should be sought.

Plasticity of Maps

We tend to think of maps as unalterable passive representations, but Merzenich described experiments which indicated the potentially plastic nature of the map in the somatosensory cortex (Merzenich *et al.*, 1983). He studied the effects on the topographic map in monkey somatosensory cortex of manipulations such as median nerve section followed by reinnervation, transposition of nerves in the hand, and amputation of a finger. The results showed an immediate unmasking of a map of parts of a finger (e.g. hairy skin) in territory previously occupied by a representation of other parts. This was often followed by changes in representation of the areas surrounding the deafferented part, such reorganizational changes being more variable in area 1 than in area 3b. However, the 'new' representations were as orderly as the ones they had replaced. Subsequent reinnervation of the affected part led to a gradual reinterpolation of a representative of this part into the new topographic map. A possible mechanism underlying these processes will be suggested later, but similar dynamically maintained maps, susceptible to being modified by disturbances in the peripheral receptor sheet, may also occur in the dorsal column nuclei.

Merzenich also described a linear relationship in the distance between units in area 3b and the degree of overlap of their receptive fields (Merzenich *et al.*, 1983). The remapping of a topographic region following such experimental manipulations was accompanied by a return to their normal linear relationship when the new map was established. Borders between major topographic subdivisions (e.g. hand and face) were not crossed by these changes. Moreover, the work of Mountcastle and his colleagues on the parietal cortex (Mountcastle *et al.*, 1975) suggests that the representation may be dynamic, changing with time and antecedent activity, and involving the behaviour of the animal as well as attentional mechanisms.

But what allows the map to be modified? The answer may lie, at least partially, in the effects of activity in layer I, which Crick believed to be the single feature that characterizes all areas of the cortex. The input fibres to this layer disregard areal borders and may be, as Mountcastle thought, 'state control' fibres, responsible for controlling the excitability or modifiability of pyramidal cells by diffusely projecting monoaminergic pathways (Crow, 1968; Kety, 1970; Pettigrew, 1978; Moore and Bloom, 1979). Some may arise in centres such as the locus coeruleus (Gatter and Powell, 1977) or the raphe nuclei, suspected of controlling attentional mechanisms, and may be uniformly distributed throughout the cortex. Others may be gated subcortically, so that different regions of the cortex are influenced differently, since the so-called 'nonspecific' input to thalamus is known to show a relatively crude regional organization.

Sakata, in discussing the parietal cortex as a centre for space perception (Mountcastle *et al.*, 1975), thought that a topographic representation of the receptor sheet may be insufficient for the perception of self and the environment, for the world is a three-dimensional space whereas the receptor sheet and topographic maps are two-dimensional. Moreover, since we move freely and are interested in objects in motion, the representation in the cortex must be dynamic.

Whether anatomically or functionally related parts of the body surface are mapped contiguously in the cortex, whether the maps are plastic or static, there is little doubt that there are profound differences in the maps between one area and another. Merzenich raised the fundamental question of what is the 'glue' or organizing principle that holds these maps together? Is such a principle common to all areas? This raised the possibility that there is a basic unit in the cortex that performs the same set of operations in each area.

Modular Structure and Function

Mountcastle thought that the striking homogeneity of the monkey cortex up to 110 days of gestation suggested that there was such a unit (Rockel *et al.*, 1980). It is only after 110 days that the extrinsic connections of the cortex develop and cytoarchitectonic differences begin to appear. Thus he thought that the general operation carried out by the cortex is the same, and differences between areas may reflect the different extrinsic connections. Therefore the fundamental question is: What is this operation being carried out by the cortex?; perhaps the detection of associations, or covariation, may after all prove an adequate answer. The question that obviously follows is: How do the elements in the cortex perform their function? Is there, in other words, a repetitive unit in the cortex, of known anatomical organization, which performs a basically uniform operation, but one which varies from area to area or region to region, according to differences in extrinsic connections?

Szentágothai discussed the concept of a cortical module (Szentágothai, 1978) which he thought of as 'a piece of neurotissue', repetitively inserted into the cortex in a similar way to how he imagined printed circuits were put in a computer. There might be as many different types of module as there are different sensory systems. A module should, he believed, have anatomical reality. Some cortical modules do have such reality, such as those 200 to 300 μm in diameter (Szentágothai, 1978, p. 222), and also the 'barrels' in lamina IV of somaesthetic cortex of rats (Woolsey and Van der Loos, 1970). But on the other hand 'orientation columns' in the visual cortex seem to have no anatomical, as opposed to functional, demarcation. Note that the minimum spread of a single thalamic afferent fibre is 300 μm while the widths of the orientation column are only 30 to 50 μm. Orientation columns therefore do not seem to correspond to anatomical modules. Mountcastle, who said he believed there are modules in the cortex and that they are about 400 μm wide, thought that the thalamocortical afferent, the anatomical reality, does not define the orientation column or any other cortical column. It is clear, however, that the ocular dominance stripes in primary visual cortex are defined by the spread of the geniculate afferents in lamina IV, at least in the adult monkey. Whitteridge's results on combined morphological and physiological studies (Gilbert and Wiesel, 1979; Martin *et al.*, 1983) showed no evident correlation between cell morphology and response property, thus reinforcing the view that to seek for an anatomical substrate for all physiological properties may prove to be a difficult exercise.

An example of a module, which might serve as a basis for thinking of modules in general, was discussed by Crick. This is the barrel field in the somatosensory cortex of rodents (Woolsey and Van der Loos, 1970). In layer IV of this cortex each 'barrel' is marked out by an encircling 'cell-dense net' of diameter 100 to 400 μm. Each group of cells, forming a barrel, is associated with a single facial vibrissa and interaction is strong among cells of the same barrel, and weak with neighbouring ones. If only one vibrissa is stimulated the deoxyglucose uptake is most obvious in all layers of the corresponding barrel. Here then is a somatosensory cortex organized into (imperfect) modules, but this probably reflects the modular organization of the receptors. It is less obvious why the visual cortex should be organized into modules because the visual field is not modular.

The patterns of cytochrome oxidase activity, shown in monkey striate cortex (Hendriksen *et al.*, 1981; Horton and Hubel, 1981), suggest that area 17 in primates is based on modules of some sort. But patchiness in itself, whether observed in cytochrome oxidase activity, deoxyglucose activity, or anatomical connectivity, does not necessarily prove that the cortex is modular in organization. Modularity implies that most of the general features of the neuronal arrangement repeat in a fairly regular manner. Thus the test of modularity is that many distinct features repeat in step with each other, an organization hinted at for area 17, but whose details are still not clear there or in any other cortical area in primates.

Thus, one hundred years after the initial debate about cortical localization, arguments about what it is that is localized continue, and the progress made can perhaps be judged partly by the refinements in the questions that we ask. One additional item of progress no-one will doubt: we now have much better techniques for answering the questions. It is interesting to note, however, that the original method, that of studying and trying to explain the deficits of function associated with specific lesions, is still capable of yielding interesting results, and is in a sense the final arbiter; if you cannot show the expected deficits of function after a local lesion, you probably have not got the right answer about what function that local region performs. Furthermore, only limited progress has been made towards understanding the other characteristic of animals suffering cortical damage that, in addition to the paucity of defects, so impressed Goltz in the last century, namely, the restitution of function in the weeks and months following the cortical ablation.

FUTURE POSSIBILITIES

We now try to spin together some ideas about the cortex in a more logical order, aiming to present a coherent view of what it actually does. It will be obvious enough that this attempt is speculative and grossly incomplete, but the only way to make progress in understanding the mass of information that is so rapidly accumulating about the brain is first to speculate about its important functions, and then for the wrong speculations to be falsified and eliminated by experimental evidence. We present this section in the form of suggested answers to four questions, followed by the outline of a model to explain how a small portion of cortex may perform its postulated prime function.

What is the Basic Operation of the Cerebral Cortex?

Mountcastle raised this question, which is certainly fundamental even if it should turn out that there is only a very broad similarity in the function of different areas. These different areas of course have different inputs and outputs so it would be easy to make their functions appear different; but in so far as there is any similarity in the pattern of local connections, the operations performed in different regions are surely likely to have something in common, and this is what we must first seek. Discussion and speculation on this point has perhaps been inhibited by the vast apparent difference between the primary projection areas and the traditional association areas of Flechsig (1901), but as we shall show, this difference may not be as great as is supposed.

First, there is a function performed by the cortex that, important though it is, is not the one we are looking for: this is the redistribution of information from one cortical locality to other parts of the brain, including other places in the cortex. As has already been mentioned, the destination of these connections is associated with the layer of the cortex in which the cell bodies lie. In so far as it is true that cells with one type of selective property are arranged in columns or clusters that pass through all laminae from pia to white matter, the type of information distributed from a given locality is the same for all laminae. This is not strictly true because there are some distinct functional differences between the cells commonly found in different layers, but the main selective properties are the same, so it is probably fair to say that the basic operation is similar for each lamina, modified slightly in accordance with the requirements of the particular destination of cells in particular layers. We must note that cortex performs this redistributive function, but most of us would like to think the cortex does more than simply disseminate information.

The operation that is of overwhelming importance for all higher neural functions is the detection of associations. What is needed in order to build up more elaborate behaviour on a set of fixed reflex responses to fixed classes of stimuli is the ability to recognize that in one set of circumstances one response to a stimulus is appropriate, whereas in another set of circumstances a different response to the same stimulus is required; and for this it is necessary to detect, not just the occurrence of the stimulus, but its occurrence in association with another event or events signifying that the circumstances have changed. The words hitherto used to describe the role of the cortex are all unconscionably vague and undefined—'the seat of intelligence', its 'unifying action', the 'source of the will', and so on—but surely this detection of associations is an operation without which none of these higher functions would be remotely possible. We therefore think this could be the basic operation Mountcastle was seeking, but we first need to refine the concept of 'associations'. MacKay suggested the term 'covariation', and this brings us closer, for it is changes that stimulate our senses, and things that change together are certainly important to us. But the cortex cannot possibly detect all forms of association or covariation, for the following reason. If there are N possible events, there are $(N^2 - N)/2$ different pairs of events, and 2^N different associations of any size; these numbers are unimaginably large for values of N corresponding to the number of events that might be signalled even in the tiniest brain, or in a very small part of a larger brain. It is therefore rather unhelpful to say that the cortex is interested in associations generally, though the hypothesis has one attractive feature: it might immediately explain why such an enormous expansion of the cortex, the 'neopallial explosion', was an evolutionary necessity once the brain undertook the task of detecting associations. But to make the concept more useful we need to specify the subclass of associations that is particularly important for the control of behaviour.

The kind of association that we think the brain needs especially to detect is that described in detective stories as a 'suspicious coincidence'—an unexpected combination of occurrences that seems to require a causal explanation because it would be unlikely to occur by chance. It is the statistical operation that we want to draw attention to, not the high level conscious process that goes on in the detective's mind. We think that nerve cells use the same inductive logic as the detective, and that statistically significant coincidences are the informational fodder that they grab hold of and devour to build higher perceptual concepts and more complex forms of organized behaviour. The proposal is that cortex does not detect any type of association or covariation, but only those coincidences that would be unlikely to occur by chance and therefore imply another cause.

This may seem very far removed from anything that we actually know the cortex does, so the first point to make is that the elementary types of pattern recognition performed in some primary projection areas fit in with this idea of coincidence detection. The detection of orientation in V1 implies the detection of coincident excitation of two points at least, for less than two do not define an orientation. Similarly determining the direction of movement requires detection of the coincidence implied by a sequence of at least two events, and also the detection of the disparities involved in stereopsis requires the detection of a binocular coincidence. Furthermore all these must be 'coincidences' in the sense referred to above: orientated edges, moving stimuli, and paired excitations at small disparities must all occur with frequency higher than expected from first-order probabilities, so to the naïve brain they are 'suspicious coincidences' requiring a causal explanation. All of these types of coincidence are detected by cells in primary visual cortex, and some of them can also be paralleled in other primary sensory projection areas.

The equivalent operation in motor cortex is not so easy to see. This cortex is the output channel of complex networks which are believed to be engaged with it in the programming of movements, and which include other cortical areas, basal ganglia, cerebellum and thalamus. In primates its most bulky inputs and outputs are those related to the hand. We should not expect its function to be the detection of significant coincidences in the sensory sphere, but rather the subconscious governing of combinations and sequences of learned movements, especially those of tactile exploration, prehension of moving as well as stationary objects, and manipulation. Its corticocortical outputs to 'sensory' and 'association' areas would provide those areas with plenty of coincidence-detection fodder from the sphere of movement. Its intrinsic neurons are foci of convergence of corticocortical and thalamocortical inputs bringing information from the moving muscles, joints and skin (Lemon, 1981*a*, *b*), as well as programmed 'commands' for movement. Conrad (1978) appropriately described the motor cortex as 'a primary device for fast adjustment of programmed motor patterns to afferent signals'.

How might this be achieved? Let us imagine the motor cells of the cortex each being activated semiautonomously by influences from remote parts of the nervous system, brought to bear on them by convergent corticocortical and thalamocortical afferents. Certain patterns and sequences will occur more often than expected from the frequencies of the components taken individually: cell *a* controlling one muscle group will frequently fire with cell *b* controlling another group, and in accordance with our notion that cortex detects suspicious coincidences, this association will be detected by a cortical neuron in that region just as orientation, corresponding to coincident activation of two or more inputs from the LGN, is detected in area 17. Alternatively *a* may commonly fire before *b*, and this sequence will be detected just as direction of motion is detected in area 17.

The coincidence-detecting hypothesis thus begins to explain how the ordered parallel and sequential activities that correspond to a controlled movement might be represented among the cells of motor cortex. It does not explain how such a coordinated movement could be created by activation of cells in motor cortex, but it should be noticed that, in a system with the potentiality for strong negative feedback, the recognition of a goal is a very important step. Suppose, for instance, that the cells detecting *unwanted* movements were suddenly empowered to exert extremely powerful inhibition on all the motor cells of a region: then the desired movement would be the only one that *could* occur. The intermingling of sensory information of course greatly increases the richness of information about coincidences that is available in motor areas.

It may be worth classifying types of coincidence in an outline scheme that takes account of the known anatomy. Primary coincidences are those detected in the primary projection areas. They must be local in nature (local orientation, local movement, disparity) because a high density of connections between neurons is only possible on a local basis. Secondary coincidences between more remote parts of the sensory field require a secondary projection in which the remote parts are represented closer to each other. The detailed pattern of these projections would facilitate the detection of particular types of coincidence by representing close together in the cortex types of event that are related, not by topographical proximity, but by some other aspect of the stimulus such as colour or direction of movement. The pattern of projection offers a way of simplifying the detection of coincidences that would otherwise seem extremely difficult to pick out, and it is a challenge to think of a means of reprojecting patterns that would, for example, make bilateral symmetry readily detectable, or that would facilitate the classification and recognition of images of faces.

Higher order coincidences would be of several types, including those between second-order coincidences, and those between different modalities. A particularly important category is the coincidence between emotion-producing events, especially rewards and punishments, and initially neutral sensory events. These must be of such overwhelming importance to an animal that we wonder if the diffuse projection systems to the cortex have the role of saying 'The events that have just happened, or are happening now, or are about to happen, are especially important, perhaps even for survival'. If the diffuse projection systems have a special overriding control on the selection of which coincidences are detected we can begin to see how the mapping and connectivity of cortex might be moulded in each individual to the hedonistic requirements of his environment.

The possibility that the cortex is the principal organ for detecting coincidences acquires much greater generality once it is realized that this operation is important in primary projection areas and motor areas, as well as for conditioning and other forms of learned behaviour. Some such function has long been thought to occur in Flechsig's association areas, but if we refine the idea to that of detecting statistically significant coincidences we see that it could be the basic operation of all parts of cortex.

What is the Cortical Language?

Coincidence detecting may be the basic operation, but how are the input events signalled, and how is the occurrence of a coincidence expressed? MacKay pointed out that a given nerve cell in the cortex receives input from a very large number of other cells, many of them close neighbours, with a few lying at considerable distances. It would be very hard to believe that a functionally sensible outcome could arise from these connections unless the communications transmitted down them followed a set of conventions, and these conventions might be termed the cortical language. It could perhaps be maintained that every single connection is a law in its own right, and has its own special meaning, so that there are no general rules in this language and nothing to be gained by terming it such. But the irregular branching pattern of an afferent input to the cortex does rather suggest that an impulse arriving down that fibre broadcasts some piece of news into a cortical region; the region might be quite small, but would nonetheless contain many thousands of cells. MacKay's idea was that some general principles for employing impulses would be necessary if such news was to be intelligible, and we think that one possible principle can be defined; furthermore we shall show how its use might facilitate the role of cortex as coincidence-detector.

Perhaps the people round a conference table provide an analogy to the cells in a small cortical region, and there are certainly necessary conventions to allow effective mutual communication at the conference table. Every utterance is broadcast to the whole table, and the first rule is for everyone to keep generally silent; without that convention communications could not even be heard. A second is that, when silence is broken, the duration and strength of an utterance should be roughly proportional to its importance. We can hardly expect nerve cells to talk to each other in a specific language like English, but even general conventions of the above sort, though too rudimentary to call a language, might prevent cortical cells suffering the equivalent of being deafened or being bored, and it must be very important to establish whether such conventions exist.

There is little doubt that nerve impulses are the elements of communication between cortical nerve cells, at least over distances greater than a millimetre or two; the conference table rules proposed above suggest that impulses should be used sparingly, and that when they are used each one should carry its due weight. According to Uttley (1979) this due weight should be measured in terms of Shannon-type information, which strictly interpreted would mean that each impulse should signal the same change in the log of the *a priori* probability of some input event. More loosely it might be said that good housekeeping in the nervous system demands that the principle of 'economy of impulses' (Barlow, 1969*a*) should be practised. The narrow dynamic range of nerve fibres, considered as communication channels, makes this especially important; if impulses were squandered needlessly it is difficult to see how any messages could be transmitted at a reasonable signal/noise ratio. There is in fact some evidence that these principles are heeded at levels below the cortex, and that messages in optic nerve and tract are already coded so that events with a very low prior probability cause many impulses whereas those with relatively high prior probability cause few (Barlow, 1969*b*, 1980). But let us see how attention to these principles may be more than good housekeeping and may facilitate coincidence detection.

Now a coincidence is suspicious in the detective story sense if $P_{AB} >> P_A \times P_B$, where P_A and P_B are the prior probabilities of events A and B considered separately, and P_{AB} is that of the joint occurrence of both of them. Any of these quantities might be computed in a region where signals for A and B are arriving, provided that the combined event is also detected whenever it occurs. But this presents a serious problem, for it seems that it would be necessary to detect the occurrence of *all* coincidences in order to calculate their probabilities and find out which of them are suspicious. As we have seen there is a vast number of possible coincidences, many of which are likely to be of no interest whatever, and it seems implausible that the cortex would dissipate its hardware by devoting it to the detection and counting of all of them.

There is one neat way of reducing this problem. If P_A and P_B, etc., are all small, then any coincidental occurrence of two (or more) events that take place with a frequency anywhere near that of the events themselves is likely to be a significant coincidence. This is simply because the product $P_A \times P_B$ (or of more of them) is necessarily much less than each probability alone, so if P_{AB} approaches P_A or P_B it certainly exceeds their product by a big margin. Hence, provided that P_A and P_B are small, the problem for the cortex is simplified to that of detecting *any* coincidence that occurs reasonably often; according to the hypothesis such patterns are ones that the cortex should detect and signal, so it would be expected that some cells become selectively sensitive to them and respond to no other input patterns.

There is an analogy here with the problem of determining disparity in the pair of images provided by the two eyes. If we take a point in one image and try to search for the point corresponding to it in the other image, our first inclination might be to look at the points with the same luminance value in the other image. But, except for extreme luminance values, there are a vast number of points at any given luminance level, and this is therefore a poor way to attempt to identify the parts of the two images that correspond to the same object in the visual fields of the two eyes. It is better to pick a pattern feature in one image that has a low prior probability, and then search for the occurrence of the same pattern feature in the other image, and V1 appears to use this principle, orientated lines and edges providing the requisite features of low prior probability (Barlow *et al.*, 1967). It is much easier to detect important coincidences when the prior probabilities of the separate events are low, but while it is important to pick a feature that has a low prior probability, it would be useless to pick features whose prior probabilities are too low, for then they would hardly ever be used. Suspicious coincidences that actually occur are the only kind that are any use to detectives, or the cortex.

How might the cortex be set up so that it detects the suspicious coincidences that actually occur? We have some evidence on this from the well-known effects of restriction of visual experience in the critical period. To take the best known example (Hubel and Wiesel, 1963, 1965*b*, 1970; Wiesel and Hubel 1963*a*, *b*, 1965*a*, *b*), a normal kitten has many cells in V1 that respond best to joint stimulation by the same stimulus through both eyes; they can thus be called detectors of coincident stimulation through both eyes. But if the kitten is prevented from experiencing these coincidences by alternating occlusion of the eyes or by surgically-induced strabismus, then the number of such cells is drastically reduced. The coincidence detectors that are present correspond to coincidences, covariations, or associations that actually occur.

Notice that coincidences cease, in a sense, to be suspicious once it is firmly established that they do occur with a frequency greater than that expected from the prior probabilities of the constituent events; the suspicion that there is an unknown cause of the association is replaced by recognition of some such connection, but the coincidence does not thereby become irrelevant; as in the case of orientated edges, movement, or disparity, the occurrence of the specific coincidence can be used as a building block, an event capable of taking part in higher level coincidences. In fact it will be an event of higher 'relative entropy' than the constituent events, and therefore eminently suitable, according to one theory, as an event for representation of our perceptions (Barlow, 1984).

To summarize this answer it has been suggested that probability and Shannon-type information play a large part in the cortical language. In the interests of good housekeeping the tokens of information exchange—nerve impulses—should be used with roughly constant and preferably high informational value. The high informational value of impulses means that the events they signal have low prior probability and this facilitates the detection of coincidences, for the cortex need only devote hardware to the detection of patterns of coincident events that occur with reasonable frequency. It is plausible to suppose that the critical period in cortical development is the period within which particular cells develop responsiveness to particular coincidences.

Why have Multiple Sensory Areas?

The suggested answer to this should now be clear: it is to facilitate the detection of specific classes of coincidence. Most connections to a particular cortical cell are from other cortical cells lying close at hand, or from input fibres which terminate in a fairly restricted region around the cell. The type of covariation, association, or coincidence that a cell can detect is therefore very strongly dependent upon where it lies and the source of the information being projected to that position in the cortex. This is where the redistributive function of the cortex can be seen to gain its importance, for this controls both the information that reaches each small region, and the destinations to which it is in turn distributed. The role of a telephone exchange is trivial if it routes messages to any possible destination according to the dial tones it receives, but it is quite a different matter if it is prewired and thereby controls which subpopulation of receivers gets all messages of a particular type.

How should such redistribution be organized? Since we have decided that the role of cortex is to detect coincidences, that is, associations of events that are *a priori* improbable but occur nonetheless, what we require from the redistribution is the bringing together of messages about events among which coincidences are likely to occur. For example, rigid objects often occupy quite a large portion of the field of view, but being rigid they move as a whole; therefore one needs to bring together movement information over substantial parts of the visual field in order that, when such an object translates, the coincident firing of local movement detectors lying at fairly distant points in the field of view shall detect the movement. The problem is of course not as simple as this because the object might, for instance, be partially concealed, or it might rotate instead of translate, but the principle does seem clear: the pattern of reprojection should be such as will bring together in small local cortical regions the information required to detect likely coincidences.

From the Gestalt psychologists we know something about what global or general characteristics of visual images are in fact brought together in this way, for they are the characteristics that enable an image to be segregated into its major components, particularly the separation of figure from ground. Proximity in the visual field is of course one such characteristic, as is proximity in the depth plane or similarity of disparity. Likewise with colour, texture and the direction and velocity of movement. Interestingly enough, the importance of defining local cues which would help to identify different parts of the same object was one of the first lessons learned from those using computers to interpret visual images, and Guzman (1968) gave these characteristics the term 'linking feature'. The role of V1 can thus be succinctly described as that of detecting linking features by local analysis of the visual image, and redistributing this information to areas specializing in each of the linking features in order for higher order coincidences to be detected there.

There is clearly much to be done to work out the implications of this idea, if correct. What is the role of area 18, or V2? Why do the other areas still have a considerable amount of topographical mapping? Can evidence for any other principles of organization, such as mapping according to nontopographical variables, be found in these other areas? But at least the hypothesis has some preliminary appeal.

Can Synaptic Rewarding Factors Explain Cortical Plasticity?

Merzenich said that, as a result of his experiments showing both plasticity and constancy in the pattern of cortical mapping, he kept on asking himself the question 'What is the cortical glue? How is continuity ensured in the map so that neighbouring regions on the skin project to neighbouring regions in the cortex?' It is perhaps worth proposing a fairly specific mechanism that would fit many of the facts.

Let us first recall the unexpected nature of the early results obtained by Wiesel and Hubel (1963*a*, *b*, 1965*a*, *b*) when they investigated the visual cortex and lateral geniculate nucleus (LGN) of visually deprived kittens. In the cells of the cortex they found clear evidence that sensory deprivation modified the pattern of connections to cortical neurons, especially if deprivation was monocular. The monocular experiment not only provided an in-built control, so that they could compare the effects of stimulating the two eyes in the same preparation and on cells recorded within a few minutes of each other, but they also showed that the undeprived eye competes for control of cortical neurons, and that the effects of deprivation are less in binocularly deprived animals in whom there is no such competition. In contrast, when they recorded from cells in the LGN, they could find little effect of either monocular or binocular deprivation on the functional properties of the cells, though they thought that it did make the responses slightly more sluggish.

When they came to look at the anatomy of cortex and LGN the results were the exact opposite. They could find no abnormalities in the cortex, but the cells of laminae in the LGN fed by a deprived eye were abnormal and reduced in size. What is unexpected here is the relation between anatomical and physiological changes: it is natural to expect that an anatomical change signifies a more serious functional defect, yet it was the LGN cells, earlier in the chain from eye to cortex, that were affected anatomically. Anatomical changes have subsequently been found in the cortex, where the ocular-dominance stripes shrink and swell in accordance with deprivation and experience within the critical period, but the clue to interpretation may still lie in the somewhat paradoxical earlier result that anatomical changes occur in the cells of the LGN, for the functional changes in the cortex may be secondary to the factor influencing the LGN cell bodies.

Suppose that the LGN cells that succeed in activating cortical neurons are rewarded and grow, whereas their companions, connected to the deprived eye, shrink because they fail to activate the cortical cells and are unrewarded. This could be explained if an unknown substance, a *synaptic rewarding factor*, is released by cortical neurons when they are activated, picked up by the recently active terminals of the nerve fibres that have caused the activity, and transported back to the cell body where it triggers nuclear changes causing growth of that cell together with the branches and terminals that picked up the synaptic rewarding factor. A feedback mechanism of this sort could be very powerful and effective in controlling growth and functional development, but how wild a speculation is it?

There is one key question for which positive evidence is available. The anatomical changes in the LGN and the functional changes in the cortex might be quite independent, each resulting simply from inactivity of the cells concerned. This would be in accord with the general view that activity is required to preserve the health of cells, and the more specific view of ophthalmologists that exercise of the pathway from a 'lazy' eye can prevent or reverse amblyopic changes. But Movshon and Van Sluyters (1981) argue against this and review much evidence showing that the cellular changes in the LGN and the functional changes in cortical neurons go hand in hand. Furthermore, Rauschecker and Singer (1981) have studied the effects of various combinations of partial and complete deprivation in one or both eyes by rearing kittens with goggles that either gave a clear view, or contained occluders, or held strongly astigmatic lenses effectively depriving an eye of vision of horizontal or vertical contours. They concluded from their results, which are the culmination of much previous work on the effects of various forms of visual deprivation (*see* Wiesel and Hubel, 1963*a*, *b*; Hirsch and Spinelli, 1970; Blakemore and Cooper, 1970; *see also* review by Movshon and Van Sluyters, 1981), that all can be explained in terms of Hebb-type synapses. This type of synapse was originally proposed (Hebb, 1949) as a mechanism of learning, and it possesses the hypothetical property that synaptic effectiveness increases if postsynaptic activity frequently follows presynaptic activity, and decreases if there is no such associated activity. The postulated synaptic rewarding factor would provide a mechanism for such a synapse.

Another important question is whether it is plausible to postulate the postsynaptic release of a substance and its pick-up by presynaptic terminals: can a synapse 'talk back' to its activating nerve fibre? The idea has a respectable history (Hamburger and Levi-Montalcini, 1949; Prestige, 1970), but the best model would be Nerve Growth Factor, for it has been suggested that this has a physiological role very much like that postulated for a synaptic rewarding factor, but acting at the synapses of peripheral fibres on their target organs (Hendry and Iversen, 1973). It is certainly the case that such substances can be picked up by nerve terminals and transported to their cell bodies, where they can have the well-known effect of activating growth (Hendry *et al.*, 1974; Hendry and Hill, 1980). It is also known that synaptic terminals of the LGN cortical afferents can pick up substances (such as horseradish peroxidase) and transport them back to the cell body.

To return to Merzenich's maps, the suggested mechanism would work as follows. Cortical afferents corresponding to regions of the body surface that were denervated or prevented from normal sensory stimulation would not excite neurons and would therefore cease to receive their normal ration of synaptic rewarding factor. The overlapping terminals from neighbouring regions that did not normally activate a given cortical cell would start doing so as the cell became hypersensitive in the absence of normal activation, and these terminals would, so to speak, steal the synaptic rewarding factor normally picked up by the now inactive terminals. The unrewarded cells would shrink, retracting their terminals, while the newly rewarded cells of the neighbouring regions would grow, expanding their terminal territories and ousting the terminals of the inactive region. Topological equivalence of the newly formed map with the old one would be likely to result from the initial overlap of innervated areas combined with graded competition for synaptic space on the cortical neurons. Whether a scenario of this sort is correct can only be determined by seeking evidence for the existence of synaptic rewarding factors, and for their release, pick-up, transport and growth-promoting cellular effects.

A Possible Model for the Coincidence-detecting Mechanism of Cortex

Start by considering a small area of cortex, perhaps 1 to 2 mm^2. The input to this area will be from cells in other parts of cortex together with thalamocortical afferents which will be prominent in the major sensory projection areas. Judging from the anatomy, each of these inputs must terminate on a very large number of cells, and each of these cells must receive input from a quite large proportion of the afferent fibres to each small region. In a grossly overlapping system like this any single afferent will tend to activate a very large number of cells, but with strengths varying from cell to cell. The same will be true of any specific pattern of activity of many input fibres, the level of excitation being of course generally higher when many inputs are active. Without any additional mechanisms the result would simply be to blur and spread out any patterns in the input, and it is hard to see that anything would be achieved. There would be general confusion and a degradation of the separability of inputs, though it is true that the associated activity of many inputs would in general cause more output activity, simply because of the greater excitation caused by many active inputs.

Now add to this arrangement a powerful mechanism of mutual inhibition acting between the cortical neurons; this might be direct, or it might be mediated by a special set of inhibitory internuncial neurons. If the mutual inhibition was so strong that a single active cell prevented all others in the neighbourhood firing, the maximum number of possible states of activity in the output would be equal to or less than the number of output neurons: any single active cell would prevent all others firing. In this way a system might be achieved in which the input states were classified into a limited number of mutually exclusive output states. Notice one particular feature of such an arrangement: if the number of output cells was greater than the number of input cells, some of the outputs would necessarily correspond to combinations of activity of inputs, so that it could be said that these output cells detected coincident activity of some subset of inputs. It is far from clear, however, that the coincidences detected would be of any interest, or that the classification achieved would be desirable in any way. The specific form of the classification would depend on the initial strengths of the input array on the output cells, which might be controlled by genetic factors, or perhaps largely by chance.

Next add a synaptic rewarding factor; as described above, this is (hypothetically) released by an output cell when activated, picked up by the synaptic terminals that caused excitation, and transported back to the cell body where it promotes growth of that cell and those of its terminals that are successfully activating cortical neurons. We cannot visualize with any certainty how such a system will develop, but can see that it provides a means of adjusting the pattern of input connectivity. Input fibres that are often active will expand their territory at the expense of less active ones, for they will more often activate output cells and thus pick up more than their share of synaptic rewarding factor. But if the number of output cells is large compared with the number of inputs, some of them will necessarily only be activated by a combination of inputs, and input cells that frequently take part in such combinations will also be rewarded. Hence, though some outputs might come to be dominated by single inputs, we would expect others to respond selectively to frequently occurring combinations, that is, to 'suspicious coincidences'.

Simulation of such a scheme would be needed to find whether it could achieve stable and interesting forms of recoding. One particularly interesting question to resolve is the relative importance of adjustments of inputs at the cellular level and at a synaptic level. It is hypothesized that the synaptic rewarding factor works at both levels, but it would be interesting to know how far the growth of whole cells on Hebbian principles might substitute for the modification of individual synapses according to Hebb's original suggestion. What is reasonable to claim is that modifiability on the scale of this model is compatible with what we know both about the genetically determined structure of the cortex, and the effects of experience. Furthermore, it might achieve the suggested basic operation of cortex, namely, the detection of significant coincidences.

CONCLUSIONS

The facts presented in London one hundred years ago perhaps gave the first indication that it would be possible to find out experimentally how the cerebral cortex works, for it was the experimental facts that showed how damage to different parts of the cortex caused noticeably different effects. To conclude, it may be interesting to conduct a sort of 'thought experiment' in which a man of considerable longevity with a passionate interest in the cerebral cortex asks questions of neurobiologists at intervals of, say, one hundred or fifty years. One hundred years ago, he might have asked: 'What does the cortex do?' and the response would have been: 'We are studying whole regions of the cortex to determine whether different parts have the same or different functions.' Asking the same question today, the response would be: 'We are studying minute areas of the cortex, small groups of cells, to discover whether there is a basic operation, a function, common to all areas of the brain.' Fifty years ago, he might have said: 'You have shown me that there are primary receiving areas and association areas, but can you tell me how the areas of the brain interact to display the integration evident in thought and behaviour?' The answer would have been 'No!' Asking the same question today, the response would be the same, in spite of the fact that we know that much of the so-called association cortex is made up of a multiplicity of sensory areas. He might have asked, one hundred years ago: 'How does the cortex see forms?' He would have been told: 'We think that there is a part of the cortex that is specialized for vision and it is through the activity of cells in that area that the brain sees forms, but we don't quite know how.' Today we might say: 'We know that there is a visual cortex and that cells in it respond to specific visual stimuli such as orientated or diffuse lights, or particular colours, but we still do not know how the brain sees forms.' Our interlocutor, getting more interested, might then ask: 'Is there a special morphology attributable to cells with particular functions? Henschen told me eighty years ago that colour cells are distinguishable by their anatomy.' We would reply: 'We have used the most sophisticated techniques of intracellular recordings and injections but cannot correlate function and structure at the level of the single cell.'

Our imaginary guest, disappointed, might wonder why it is, then, that neurobiologists today seem so confident that they will understand, perhaps within years, some of the elusive secrets of the cortex. We would tell him to return, not in fifty years, but in five because our range of facts is now so great and hence we are able to speculate, as in the last section, in ways which we could not have done even twenty years ago. This, in turn, allows us to explore new approaches, discount old ideas and pursue new ones, always with the knowledge that the one certain thing about the future of cortical studies is that there will be surprises which will alter radically our way of thinking about the brain.

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APPENDIX

Participants at Meeting held at Hertford College, Oxford, on August 4 and 5, 1981.

H. B. Barlow, University of Cambridge; F. H. C. Crick, The Salk Institute, California; A. Cowey, University of Oxford; W. Fries, Ludwig Maximilians Universität, Munich; T. J. Horder, University of Oxford; Y. Iwamura, Toho University; R. H. Kay, University of Oxford; H. G. J. M. Kuypers, Erasmus University, Rotterdam; R. Lemon, Erasmus University, Rotterdam; S. LeVay, Harvard Medical School; D. M. MacKay, University of Keele; M. M. Merzenich, University of California, San Francisco; G. Mitchison, The Salk Institute, California; V. B. Mountcastle, Johns Hopkins University; C. G. Phillips, University of Oxford; R. Porter, Australian National University; H. Sakata, Tokyo Metropolitan Institute; J. Szentágothai, Semmelweis University, Budapest; L. Weiskrantz, University of Oxford; D. Whitteridge, University of Oxford; S. Zeki, University College London.

Brain (1984), **107**, 363–368

NOTICES OF RECENT PUBLICATIONS

H. Houston Merritt Memorial Volume. Edited by Melvin Yahr. 1982. Pp. 232. New York: Raven Press. Price $36.58.

Dr Arnold Friedman in 1982 wrote in his masterly appreciation of H. Houston Merritt. 'He was a man of consequence and one of the Giants in American Neurology.' It is, therefore, right and proper that there should be published a memorial volume to commemorate the life and work of one of the most able clinicians in the United States. We are grateful to Dr Melvin Yahr who acted as Editor and also contributed a paper on Parkinson's disease in which he set out the pharmacological picture as it appears today. In an introductory Preface Dr Yahr has afforded us a personal tribute and a biographical outline of Dr Merritt's life and works, pointing out the diversity of his talents as textbook author, administrator, diagnostician and teacher. He was indeed fortunate in the early success of his pharmacological breakthrough with the development of phenytoin. Houston Merritt did not return to the laboratory, for it was obvious that his genius was of a rarer kind and lay midway between the council chamber and the bedside.

Among the contents of this volume, Dr Dewey Ziegler presents an important and worthily critical account of migraine. Dr Poser on syringomyelia is encyclopaedic, and 'goes deeply into the surface of things'. Dr Roger Rosenberg has afforded us an interesting paper on genetic variation and neurological disease. The story of phenytoin, opened in 1928 by Merritt and Putnam, has been brought up to date by Dr Mark Goldberg. Dr Burk Jubelt and his team have reviewed the problem of herpes simplex virus encephalitis. The recent recrudescence in interest in the decreptitude of the arteriosclerotic brain receives a useful critique from Dr Robert Katzman. Mechanisms in epilepsy related to critical periods in cerebral development form a serious topic, ably handled by Dr Gilbert Glaser.

At his last teaching conference as Director of the Neurological Institute, Houston was shown a 'patient' who, after he had been taking phenytoin for only 24 hours, developed every known complication including neuropathy, seizures, extrapyramidal signs and lymphoma! As Dr Rosenberg recounts, Houston quickly realized the humour of the prank, which illustrates the affection with which he was held by the resident staff.

Altogether an interesting and worthy tribute, the sole fault of this book being that it is all too brief. Houston's professional interests ranged widely and we would in particular have welcomed papers on multiple sclerosis, brain tumours and much besides.

MACDONALD CRITCHLEY

Epilepsy: Diagnosis and Management. Edited by T. R. Browne and R. G. Feldman. 1983. Pp. 376. Boston and Toronto: Little, Brown. Price $38.50.

It is the contention of the editors of this book that 'a large volume of new information in the diagnosis and management of epilepsy has been published in the past decade', and they 'have observed that physicians other than full time epileptologists are not aware of much of this'. To keep us up to date (actually not so, as there is only scarce reference to work published in the last few years) we are presented with this book of 31 chapters from 18 contributors drawn largely from the Eastern Seaboard. The book has a textbook format, and attempts a comprehensive coverage of the field. Much is made of the modern international classification of seizures, and there is a chapter devoted to each seizure type. This is a successful and useful device, and rightly emphasizes the importance of accurate classification. There are separate chapters on each of the major anticonvulsant drugs, and additional short chapters on a series of other topics, ranging from nursing management to seizures associated with alcohol use and alcohol withdrawal. I thought this was generally a well conceived design, but a book so structured is bound to suffer from multiauthorship. The problems are those of repetition, though this is lessened by repeated cross referencing, those of contradiction (the fortunes of valproate, for instance, rise and fall through the book like Atlantic rollers), but mainly those of omission. There is no detailed discussion of prognosis, the rarer causes of epilepsy (particularly the congenital or genetic diseases), the rarer forms of epilepsy (benign rolandic epilepsy or myoclonus, for instance) or of specialized investigation. These surprising omissions result presumably from the division of authorship. Other deficiencies stem perhaps from the fact that most of the 'useful new information' which stimulated publication of this book is American, and European and even Canadian work is inadequately recognized. For instance, there is no mention of chlormethiazole in the treatment of status epilepticus, or any discussion of the modern pathophysiology of myoclonus. This is not in the best traditions of East Coast scholarship, nor, incidentally, is the quality or clarity of much of the writing.

The best chapters are very good, but the overall result is prosaic. As a straightforward text on the clinical aspects of epilepsy for the nonspecialist, however, this book serves a need.

SIMON SHORVON

Epilepsy. Edited by A. A. Ward, J. Kiffin Penry and Dominick P. Purpura. 1983. Pp. 404. New York: Raven Press. Price $6.38.

The useful series published under the banner of the Association for Research in Nervous and Mental Disease has returned to the subject of epilepsy for the first time since 1946. In no way can the volume be considered to be a 'textbook of epilepsy'. The limited selection of subjects under review presumably reflects the editors' views on the growing tips of research in epilepsy.

The chapter on epidemiology and the genetics of epilepsy by Hauser, Annegers and Anderson is a succinct review of a troublesome field. There is also a useful chapter on the mechanism of anticonvulsant drugs by Woodbury, Kemp and Chow. Perhaps most valuable for those not active in pure biological research is a brief survey on the ionic basis for the electrophysiological activity of mammalian neurons.

This will prove a useful volume for broadening the horizons of those engaged in other fields, providing insights into what is clearly an active and growing area of neurological research.

ANTHONY HOPKINS

Hughlings Jackson on Psychiatry. By Kenneth Dewhurst. 1982. Pp. 178. Oxford: Sandford Publications. Price £9.00.

Although recognized, even during his lifetime, as amongst the most influential of all writers on the nervous system, many students of neurology might be hard-pressed to define Hughlings Jackson's contributions to their subject. Jackson's failure to synthesize his views in a single work or make a representative selection of his diverse papers has been partially rectified by reprinting collections of his writings on speech, epilepsy, evolution and dissolution of the nervous system (1915, 1932) and clinical topics (1925). Sir Henry Head also attributed relative neglect of Jackson's work to his modesty, prose style and advanced ideas, blaming his Spencerian views on psychology for alienating contemporary opinion.

In *Hughlings Jackson on Psychiatry* Kenneth Dewhurst describes how Jackson's early medical experience was psychiatrically flavoured by contact with Daniel Tuke and Thomas Laycock in York, later by visits to the West Riding Lunatic Asylum and through the writings of George H. Lewes, Alexander Bain and Herbert Spencer. Dr Dewhurst hints at a reluctance in Jackson to confront psychiatric illness whilst accepting that it could be approached much as other diseases of the nervous system and yoked to his principal philosophy of an evolutionary hierarchy of sensorimotor systems underlying organization in the nervous system from which the symptoms of disease could be interpreted as dissolutions leading to negative and released positive symptoms. Psychiatric symptoms could best be incorporated in his scheme by assuming a parallel relationship between mind and body and this least compromised his ambition to understand the nervous system in its entirety.

Dr Dewhurst has achieved the scholarly task of drawing together the phrases, sentences and paragraphs in Jackson's papers which deal with psychiatric disease, thereby making them accessible to others and showing that these writings supplement and contribute to Jackson's ideas on evolution and dissolution in the nervous system. In the central six chapters Kenneth Dewhurst illustrates how Jackson's concept of normal dissolutions (sleep, dreaming, somnambulism, altered consciousness) relate to the less normal (obsessions, jokes, ludicrous thoughts) and overtly abnormal (toxic psychoses, delirium, epileptic symptomatology), pointing out the predictable and nonrandom content of these pathological conditions. Jackson did not distinguish hysteria from malingering and had firm ideas on the juxtaposition of cart and horse with respect to Victorian preoccupations such as the relationship of insanity to onanism. The first and a later chapter give details of an individual case of Gilles de la Tourette syndrome and of Dr Z (Arthur Myers); through his brother (F. W. H. Myers) he was closely involved with a celebrated group of psychic researchers who successfully concealed the true cause when Dr Z died aged 41, apparently during an epileptic fit. In tracing the influence of Hughlings Jackson on contemporary and present-day European and American psychiatry, Dr Dewhurst inevitably has to make rather infrequent and arbitrary stops down the years and as with his discussion of recent work on temporal lobe epilepsy, these sections do not fit comfortably in his otherwise fluent and very readable book.

Kenneth Dewhurst's most recent study in the history of neurology reveals the essence of Hughlings Jackson's contribution to understanding the nervous system illustrated here through his work on psychiatry but equally applicable to his other clinical writings; the book is an important addition to Jacksonian criticism and will stimulate others to seek out and read the original papers.

ALASTAIR COMPSTON

Immunology of the Nervous System. By S. Leibowitz and R. A. C. Hughes. Current Topics in Immunology Series. 1983. Pp. 304. London: Edward Arnold. Price £22.50.

The increasing interest of clinicians in the immunology of the nervous system reflects the growing body of evidence that disorders of immune regulation may underlie or contribute to a number of neurological illnesses including multiple sclerosis, some forms of acute and chronic polyneuritis, myasthenia gravis, paraneoplastic myasthenia and polymyositis. This text is therefore timely. Dr Leibowitz and Dr Hughes have boldly set themselves the task of together reviewing the whole field, rather than editing contributions in a multiauthor volume. Their disciplines of Immunopathology and Clinical Neurology, respectively, make them well suited for the work.

The text contains three introductory chapters on immunopathological processes in the nervous system which include consideration of the blood-brain barrier and the nature of the immune response. Experimental animal models of neuroimmunological disease have proved a fertile field and these are discussed in some detail. Experimental allergic neuritis (EAN) is covered in the same excellent chapter as human acute polyradiculoneuritis, and the authoritative style here reflects the clinical and research interest of one of the authors. Experimental allergic encephalomyelitis (EAE) and multiple sclerosis have, in contrast, chapters to themselves which are placed quite separately in the text, leading the reader to conclude that the authors may view somewhat differently the validity of these two models with respect to their putative clinical counterparts.

A wide range of neuroimmunological diseases is covered. Myasthenia gravis (including its experimental model) and the immunology of infections of the nervous system are dealt with in separate chapters. Other neurological diseases in which the immune system is implicated are contained in two very useful chapters, and the text concludes with chapters on tumour immunity and on advances in neurobiology, which includes a discussion of the use of monoclonal antibodies and other markers for neural cell types. The text is well referenced although it is a pity that the publishers do not include the final page number of each reference.

Since the book also includes sections on immunological treatment of each of the conditions discussed, it will be particularly useful for clinicians who are looking both for a concise review of the background to the field, and some practical advice on the value of immunological approaches to therapy.

J. Newsom-Davis

Neural Models of Language Processes. Edited by M. A. Arbib, D. Caplan and J. C. Marshall. Perspectives in Neurolinguistics, Neuropsychology and Psycholinguistics. 1982. Pp. 569. London and New York: Academic Press. Price £32.80; $49.50.

This book aims to provide 'a new perspective on neurolinguistics that integrates the insights of neurology and neuroscience, linguistics and psycholinguistics, and artificial intelligence and brain theory'. After three introductory papers, four major sections are devoted to each of these fields, the contributors being some of the most eminent authors in each area of study (and almost exclusively North American). The sections are knit together by prefaces to provide the synthesis needed for this diversity of approaches.

The range is impressive. Here are, for example, descriptions of computer sentence-parsing systems (HWIM, HEARSAY), examination of the histology of the frontal association cortex in Rhesus monkeys, reviews of psycholinguistic experiments testing the commonality of language production and language comprehension, philosophical discussion of the mind-body problem, an exposition of the grammar of deaf sign language, simulation of lesions in a mathematical model, examples of the glossolalia of pentecostal charismatic believers, and case studies of aphasic patients. One senses, however, not scientists from different disciplines displaying their wares to the initiated, but searchers on a common frontier who have read widely across interdisciplinary boundaries: neurologists who respect linguistics, psycholinguists who are fascinated by neurology and neuroscientists interested in the common architectonics underlying cognition in animals and language performance in man.

Many of the chapters are elaborations of viewpoints expressed elsewhere, but some of the links made are truly innovatory. The book initiates the contribution of artificial intelligence (AI) to neurolinguistics. This contribution includes the principle of 'cooperative computation', that is, the simultaneous activity of many processes in continuous interaction, and an emphasis on the need for incorporating control systems in the dynamics of processing. The notion that language should be conceived of as an evolutionary development of more primitive abilities in animals also makes neuroscience relevant to neurolinguistics. Arbib in Chapter 25, for example, applies studies of visuomotor mechanisms in the prey-selecting frog to a neurolinguistic model of confrontation naming. Thus he derives a model which incorporates not only the psychlogical term 'visual perception' and the linguistic term 'phonemic analysis' but also the AI notion of a switching control system which includes the physiological concept of S-cells which filter activity by building up inhibition and N-cells which override these cells by monitoring temporal changes. Moreover data from brain-damaged patients tentatively allow such models to be mapped on to neuroanatomical locations of critical areas (though in this example Luria's location of the switching control area for articulation to a unilateral cortical site is used).

Earlier mixings of terminology have been disastrous, resulting in the chaos of confusion of terms from which aphasiology has not yet entirely freed itself. This new blending promises to be different. It is based on an open discussion between disciplines and uses terms which are anchored in experimental data. Not surprisingly, also, the introdution of neuroscience to neurolinguistics acknowledges the contribution of the only investigators to date to draw extensively on neurophysiology in their interpretation of aphasia syndromes, Luria and his East European adherents.

Is the ambitious aim of this book of integrating so many disciplines realized? It succeeds, not in providing answers to how language can be mapped onto neurons—an impossible target at this stage of development of the nascent science of neurolinguistics—but in showing how different sciences can gel in defining the area of search and in deciding what questions can realistically be asked in the near future. Ten years ago contemplation of such a book would have been impossible. The next ten years may see the rejection of some of the hypotheses it offers, and reduce some of its proposals to pioneering naïvety, but it will remain a landmark in the interdisciplinary development of neurolinguistics and cognitive neuroscience.

RUTH LESSER

Clinical and Radiological Aspects of Myopathies. CT Scanning—EMG—Radioisotopes. By J. A. L. Bulcke and A. L. Baert. Pp. 187. Berlin: Springer. Price DM 128.00.

This book represents an important new contribution to the study of muscle diseases and to radiology. Although skeletal radiology is well advanced, that of the muscular system is far from exploited. This monograph provides the basis for a greater understanding of the alterations in gross muscle size and tissue composition in human myopathy including muscular dystrophy. What is striking is the opportunity afforded for the first time to see the relative involvement of different muscle groups and by repeatedly studying these muscles to assess the time course of the development of pathological processes. This book provides a valuable source of information about the distribution and size of muscles during life, and by including material on other investigations of human myopathy including electromyography and function measurements, this book adds life to the images obtained radiologically. It is profusely illustrated with high quality radiographs and also illustrations which help to interpret these for the reader who is unfamiliar with such radiological appearances. Tabulated information includes classifications and data of muscle groups and of diseases affecting muscles. Details are given of means for discerning the radiological density of individual muscles (reflecting the replacement of the muscle by fat). The correlations with muscle strength and with electromyographic changes are at best of a very simple nature but still helpful. The bibliography is adequate and the index sufficient to be useful. I can thoroughly recommend this book for radiologists, neurologists, paediatricians and physiologists interested in human muscle in health and disease. The book is well presented and the price seems appropriate for a new monograph in a rapidly developing subject.

R. H. T. EDWARDS

Neuroradiology. By Edmund Burrows and Norman Leeds. 1981. Volume 1, pp. 529+14. Volume 2, pp. 352+14. Edinburgh: Churchill Livingstone. Price £95.00.

A British and an American neuroradiologist have collaborated in this work, which comprises two substantial volumes. In eleven chapters (about 500 pages) Volume 1 presents an overview of current neuroradiological practice whose discussion includes a comprehensive account of 'classical' neuroradiology. The chapters are arranged under a mixture of anatomical, clinical and pathological headings such as the pituitary region, posterior fossa lesions, head injuries and subarachnoid haemorrhage. Although this may suggest an inconsistent and somewhat disorganized layout, finding one's way about the book is easy, and repetition is not a striking problem.

The reproductions are of good quality; the scans, however, are mainly from an early head scanner and will look rather dated to many radiologists and clinicians now using third generation scanners. This, of course, is a comment, rather than a criticism, on an unavoidable problem when material is amassed over several years.

The text is written very clearly and in some detail, including many lists of differential diagnoses, and there are comprehensive lists of references after each chapter.

Volume 2 is completely different, consisting of 100 exercises in diagnosis, each presented as a clinical problem with radiographic or scan images accompanied by some pertinent questions and followed by answers with a brief discussion of the salient features, often accompanied by further examples of the condition. Although this follows the successful example of a standard textbook of orthopaedic radiology, the reviewer would prefer to see these two books published and purchasable as separate entities, rather than together. The volumes are, in fact, cross-referenced so that one should be able to 'pass the test' if the contents of the relevant chapters have been absorbed.

In short, the textbook comprises two very different volumes, the first intended as a comprehensive textbook of neuroradiology, the second a series of exercises. Both are instructive and entertaining. Much 'classical' radiology is discussed in Volume 1 which has become superfluous to current practice, but of course should be assimilated by serious neuroradiological trainees; I think that they should buy this book.

A. R. VALENTINE

Cytochemical Methods in Neuroanatomy. Neurology and Biology. Volume 1. Edited by Victoria Chan-Palay and Sandford L. Palay. 1982. Pp. 568. New York: Alan R. Liss. Price $96.00.

This book is the published record of a conference held at the National Institutes of Health, Bethesda, in June 1981, devoted to a discussion of cytochemical methods that have been, or may be, used to explore the structure and function of the nervous system. The participants were drawn from a range of disciplines; their contributions encompass both the vertebrate and invertebrate nervous system, and include studies of anterograde and retrograde transport mechanisms; histochemical, immunocytochemical and autoradiographic localization of neurotransmitters and other neuroactive substances; and sensible discussions of such matters as the value of computer asisted morphometric techniques, and the problems and pitfalls of immunocytochemistry.

While the majority of the chapters are largely concerned with describing the results of specific items of research and contain much of interest, methodology as such is not neglected, and readers who are less familiar with the field will find a number of useful and detailed descriptions of, for example, autoradiography of transmitter molecules, and the techniques used to demonstrate specific immunocytochemical localization. As a consequence the work should prove a useful source of reference to neurobiologists in general, and be of particular value to those who wish to exploit the powerful tools offered by modern cytochemical techniques to explore the functional inter-relationships of the various parts of the nervous system and their anatomical interconnections.

D. N. LANDON

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FORTHCOMING EVENT

The United States/Canada Joint Conference on Neurological Emergencies in Children and Adults will take place June 8–10, 1984 at Inn on the Park, Toronto, Ontario, Canada. The conference is sponsored by Continuing Medical Education and the Departments of Neurology and Pediatrics, State University of New York and Buffalo, and the Department of Pediatric Neurology, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada. Further information can be obtained from Rayna Dutton, CME Coordinator, Continuing Medical Education, Children's Hospital, 219 Bryant Street, Buffalo, New York 14222.

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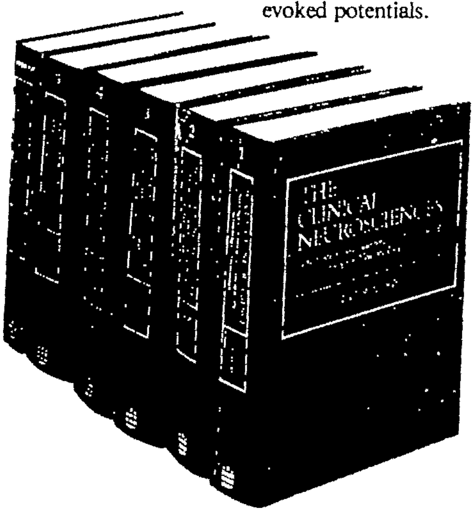

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INITIATION AND EXECUTION OF PREDICTABLE AND UNPREDICTABLE MOVEMENTS IN PARKINSON'S DISEASE

by C. A. BLOXHAM, T. A. MINDEL *and* C. D. FRITH

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SUMMARY

Nine patients with Parkinson's disease were compared with aged-matched normal controls on a tracking and a reaction time task. In the tracking task, subjects had to follow a target moving either predictably or unpredictably at various frequencies. There were no differences between the groups on this task. Both groups were able to use the predictable target movements to eliminate the lag between the target movements and their own movements, indicating that they could emit preprogrammed responses which did not depend on visual feedback. The reaction time task also contrasted predictable and unpredictable movements since the subjects were sometimes told in advance which finger they would have to lift in response to the imperative signal. The patients were significantly less able than controls to use this predictability to reduce their reaction times. It is concluded that parkinsonian patients can use prior information to control the form of a preprogrammed movement, but cannot use this information to help initiate such a movement.

INTRODUCTION

The abnormalities of movement that characterize Parkinson's disease are well known and widely believed to be the consequences of damage to the nigrostriatal pathway and subsequent dopamine deficiency in the striatum. Each of the cardinal signs of this illness has received increasing attention and several attempts have been made to discover their possible pathophysiological basis (Marsden, 1982). The most disabling feature, however, is undoubtedly hypokinesia, held by many to be the primary symptom of basal ganglia dysfunction (Denny-Brown, 1968). Earlier studies were directed towards elucidating the different facets of this symptom such as initiation difficulties (Draper and Johns, 1964), slowness of movement (Joubert and Barbeau, 1969), and problems in stopping or changing motor patterns (Joubert and Barbeau, 1969, Angel *et al.*, 1970). More recently Hallett and Khoshbin (1980), emphasizing the difficulties parkinsonian patients have in performing ballistic movements described, on the basis of EMG studies, a possible 'derangement in energising muscles' that might represent a physiological mechanism underlying bradykinesia.

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Other workers have interpreted the clinical features in terms of disturbed central control mechanisms, reflected by studies showing that parkinsonian subjects have difficulty in performing two actions simultaneously (Schwab *et al.*, 1954). Indeed, from clinical observations of parkinsonian patients, Marsden (1982) concluded that the normal role of the basal ganglia is the 'automatic execution of learned motor plans'.

In the same vein, Flowers (1978*b*) reported that patients demonstrate a failure to employ the normal strategies of prediction during visual tracking tasks and cannot therefore utilize an 'internal model' of external events in carrying out motor activities. He suggested that this results in the loss of 'skills' which leads to a greater dependency upon sensory, especially visual, information.

A relevant concept is that of motor programs (Keele and Posner, 1968) which account for the improvement in performance of any movement in which an 'open loop' mode of control can be used, such as the tracking of a regularly moving target. In this situation the subject can plan and execute his movement in advance and in anticipation of the target's movement. In contrast, only feedback control, or closed loop strategies are possible when the target movement is irregular. Here the subject can only plan and execute his movement on the basis of how the target has just moved.

The implications of Flowers' work is therefore that patients with Parkinson's disease are unable to make use of such programs during motor activity. However, clinical features such as kinesia paradoxica suggest that the specific difficulty may be in acquiring access to motor programs that in themselves are relatively intact, since in certain circumstances severely impaired patients can execute complex movements in a normal manner.

We have attempted to demonstrate that the performance of parkinsonian subjects on two different tasks is consistent with the idea that they can execute preprogrammed movements, but have difficulty in initiating them without the help of an external trigger. During the first experiment predictable and unpredictable movements are compared in a pursuit task. To track a moving target using feedback the subject must first observe where the target has gone and then make the appropriate movement to catch up with it. As a consequence of his relatively long reaction time there will always be a detectable delay between an unexpected movement of the target and the corresponding corrective movement of the subject. If, however, the path of the target is predictable then the subject can initiate his movements in advance and in anticipation of the target. Young (1962) developed a simple method for generating predictable and unpredictable target movements and for assessing the lag in the subject's response. He demonstrated that for an unpredictable target there was an increasing lag in the eye movement response as the target velocity increased. For predictable targets, on the other hand, there was no increase in lag with increasing target velocity. Control of a movement in anticipation of the target cannot be achieved by feedback; it must be achieved by preprogramming the response. Thus if patients with Parkinson's disease can only control their movements by feedback they should not be able to benefit from predictable target movements by anticipating them.

The second experiment involves the measurement of reaction times with and without prior knowledge of the movement required and concerns selection and initiation, rather than execution of a response; we would anticipate that if patients are unable to use prior information to select a motor program before execution of the task, they should not in turn be able to reduce their reaction times when the movement required is known in advance.

EXPERIMENT 1

Method

Subjects had to track a target which moved in two dimensions on the face of a VDU with a maximum amplitude of 10 cm. The target was a 4 mm square and the subject-manipulated marker was a cross which fitted exactly inside the square. The subject's task was to match the movement of the target as closely as he could, keeping the cross, if possible, inside the square. The position of the cross was controlled by means of a 17 mm long joystick which the subject held in his preferred hand. The subject's elbow rested on a foam rubber pad and thus control of the joystick required movement of the wrist and forearm.

Control of target movement. Movement of the target in the horizontal and vertical directions was controlled independently. For each of these directions of target movement the position of the target every 25 ms was determined from a combination of sine waves. For predictable tracks the vertical and horizontal components were single sine waves of the same frequency, but 90 deg out of phase so that the target moved in a circle in a clockwise direction. Frequencies ranged from 0.1 Hz to 1.2 Hz (*see* Table 1). For the unpredictable tracks three sine waves were combined for each direction of movement. These three sine waves were of unequal and unrelated frequencies (*see* Table 1). The irregular pattern of target movement that resulted was essentially unpredictable since it did not repeat for 5 min. The highest frequencies for the four unpredictable tracks were identical to the single frequency of the corresponding predictable track. Thus the lag shown by the subject for the same frequency in predictable and unpredictable tracks could be directly compared. Control of target movement was implemented by a PDP-11 computer.

Recording of tracking response. Two voltages indicating the horizontal and vertical positions of the joystick were fed into the computer *via* A/D converters and thus controlled the position of the cross. Position of target and subject cross were recorded every 25 ms.

TABLE 1. TRACK COMPONENTS

		Predictable		*Unpredictable*					
		Horizontal	*Vertical*	*Horizontal*			*Vertical*		
Frequency	1	0.20	0.20	0.20	0.11	0.04	0.20	0.09	0.06
(Hz)	2	0.40	0.40	0.40	0.21	0.09	0.40	0.19	0.11
	3	0.80	0.80	0.80	0.42	0.18	0.80	0.38	0.22
	4	1.20	1.20	1.20	0.63	0.27	1.20	0.57	0.33

Procedure

Subjects were first presented with a very slow predictable track (0.1 Hz) which was used as a trial run. Thereafter each predictable track was followed by an unpredictable one with matching highest frequency. The tracks were presented in order from the slowest to the fastest. A single run with each track lasted one minute and the subject had a 3 min rest between each run. Subjects were told in advance whether a track would be predictable or not and were also told that the predictable track would be in a circle.

Analysis of performance. The first 30 s of each 1 min run were discarded, since the frequency analysis required that the sequence of samples should be in a relatively 'steady' state. The following 512 samples (12.8 s) of both subject and target positions were subjected to a Fourier transform for the frequencies used to generate the target movement. This was done for the horizontal and vertical components separately. Frith (1973) had found that only those frequencies present in the target were present to any extent in the responses produced by subjects when performing this task. The phase lag of the subject was estimated from the differences between the phase of the target and the phase of the subject. Phase lag was measured in degrees such that 90 indicates a lag of ¼ cycle and 180 indicates a lag of ½ a cycle. As a consequence of relating lag to frequency the same delay in terms of time will appear as small lag at a low frequency and a large lag at a high frequency. The amplitude ratio (AR) was also measured. This gives a value of 1.0 when the amplitude of the movements produced by the subject is equal to that of the target. If the subject's amplitude is smaller than that of the target then the AR is less than 1.0. Groups and conditions were compared using analysis of variance with repeated measures (predictability and frequency).

Subjects. Patients with a severe impairment of movement control due to Parkinson's disease would obviously find this tracking task extremely difficult to perform. As a consequence they would perform any version of this task, whether predictable or unpredictable, worse than age-matched controls. However, the demonstration of a global quantitative impairment in Parkinson's disease would be of little interest. Information about the precise nature of the problem with movement control can only come from the demonstration of qualitative differences between patients and controls. Our prediction from Flowers' experiments is that patients with Parkinson's disease are unable to execute the preprogrammed movements which are possible when tracking a target which moves in a predictable manner. Given this hypothesis the ideal selection strategy would be to choose a group of patients and controls who were matched on their performance when tracking an unpredictable target. If the hypothesis was correct, then, in spite of this close matching, the patients should be impaired relative to controls when tracking a predictable target. For this reason we deliberately excluded from our patient group those more severely impaired people who had considerable difficulty with the tracking task (i.e. less than 5 per cent time on target).

TABLE 2. CLINICAL ASSESSMENT OF DISABILITY IN THE PARKINSONIAN GROUP

Subject	*Sex*	*Age (yrs)*	*Duration (time from diagnosis)*	*Tremor*	*Rigidity*	*Bradykinesia*	*Social disability*	*Drugs*
1	M	56	2 yrs	Nil	Both arms	Moderate	Independent	Sinemet
2	F	70	11 yrs	L arm R mild	Both arms	Slight	Independent	Sinemet Kemadrin
3	M	50	8 yrs	Nil	Slight, both arms	Moderate	Independent	Sinemet (+propranolol)
4	F	43	1½ yrs	Nil at rest	L arm	Nil	Independent	Sinemet
5	M	43	2 yrs	Nil	L arm	L arm	Independent	Sinemet
6	M	44	2 yrs	L arm + L leg	L arm R, mild	Slight	Independent	Nil
7	F	74	2 mo.	Slight	Slight, both arms	Mild	Independent	Sinemet
8	F	69	4 yrs	Nil	L arm	Nil	Independent	Sinemet (+propranolol)
9	F	68	2 yrs	Nil	Both arms	Slight	Independent	Nil

The parkinsonian group comprised 9 subjects, 4 male and 5 female. They were all outpatients with a history of the disease lasting at least eighteen months. Details of symptoms at the time of testing and the treatment regime are shown in Table 2. They were aged between 43 and 70 years with a mean of 57.4. All had been contacted through the Parkinson's Disease Society and had volunteered to take part in the experiment. All these volunteers were right-handed and they used this hand to perform the tracking task.

The control group consisted of 11 volunteers from the League of Friends at Northwick Park Hospital. There were 6 females and 5 males aged between 43 and 74 years with a mean of 60.8. All but one female were right-handed. All controls used their preferred hand to perform the tracking task. As a result of failure of apparatus, data from 1 subject in the Parkinson group and 2 subjects in the control group were lost.

Informed consent was obtained from every subject.

TABLE 3. MEANS AND STANDARD ERRORS FOR AMPLITUDE RATIO AND PHASE LAG IN PARKINSONIAN PATIENTS AND CONTROLS

				Unpredictable	
	Frequency (Hz)	*0.2*	*0.4*	*0.8*	*1.2*
Amplitude ratio	Patients	0.93±0.04	0.95±0.04	0.74±0.08	0.64±0.09
	Controls	0.94±0.06	0.85±0.03	0.80±0.07	0.59±0.09
Phase lag (deg)	Patients	15±4	21±4	51±9	75±7
	Controls	9±3	18±4	41±6	91±9
				Predictable	
Amplitude ratio	Patients	0.94±0.04	0.89±0.05	0.79±0.08	0.57±0.08
	Controls	0.85±0.03	0.74±0.05	0.66±0.07	0.53±0.07
Phase lag (deg)	Patients	7±2	6±5	10±3	26±14
	Controls	1±2	7±3	6±5	51±17

Results

Table 3 shows the mean phase lags and amplitude ratios for the various conditions. For the raw phase lag data there was a strong relationship between mean and standard deviation with high means being associated with high standard deviations (*see* Table 3). This relationship was eliminated by taking the square root of the absolute phase lag, i.e. sign (square root (absolute phase)). By this means the data were rendered suitable for analysis of variance. (In fact exactly the same results were obtained by performing an ANOVA on the raw data.) There was a significant interaction between predictability and frequency (F(3,45) = 4.78, *P* (Greenhouse-Geisser correction for repeated measures) < 0.01). This is illustrated in the figure. The lag is greater for the unpredictable tracks at all frequencies, but this difference is much greater at the high frequencies. Lag on the unpredictable tracks increases steadily with increasing frequency. Lag on the predictable tracks hovers around zero

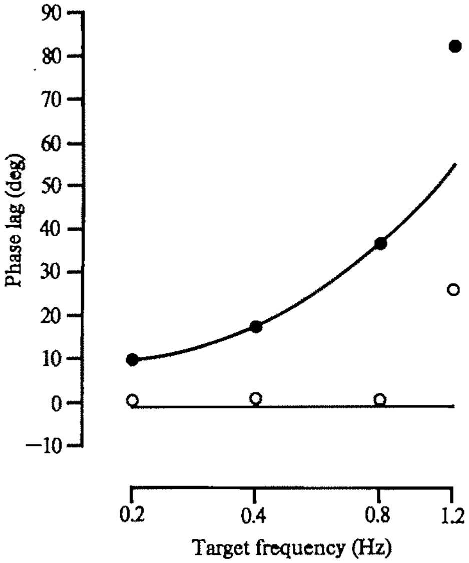

FIG. Mean phase lags for parkinsonian patients (8) and control subjects (9) combined. The y-axis has the phase lag of the subjects behind the target in deg, the x-axis the frequency of movement of the target in cycles/s. The closed circles are the phase lags for unpredictable targets, the open circles the phase lags for predictable targets. The solid lines are the best fit curves for the three lowest target frequencies assuming a constant lag in ms; this was 130 ms for the unpredictable targets and 0 ms for the predictable targets.

up to one cycle per second and then shows a sudden increase. There was absolutely no difference between the groups in the effect of predictability on lag (F(3,45) = 0.96), or any other effect. Essentially the same results were found for amplitude ratios. There was a decrease in the amplitude of movement as the target frequency increased (*see* Table 3), but there were no differences between parkinsonian patients and controls on this measure.

EXPERIMENT 2

Method

Subjects responded to the command 'GO LEFT' or 'GO RIGHT' presented on a VDU by lifting their left or right index finger. Either 250 ms or 2000 ms prior to this command 1 of 3 possible warning signals appeared: 'READY', 'READY LEFT' or 'READY RIGHT'. With the warning signal 'READY' the subject did not know in advance which movement he would have to make, which is analogous to the unpredictable track in Experiment 1. With the warning signals 'READY LEFT' or 'READY RIGHT' the subject knew in advance which movement he would have to make which is analogous to the predictable track. The subject's index fingers rested on two touch-sensitive pads. A relay was closed as soon as either finger ceased to be in contact with a pad and this closure was detected by a PDP-11 computer which also controlled the presentation of the warning and imperative signals.

Procedure

The 8 conditions (warning x hand x delay) were presented in a balanced design so that in each block of 24 trials each condition appeared 3 times in a random order. Each subject first performed 1 block of trials for practice and then, when the task requirements were clear to him, performed 3 more blocks of trials the data from these being retained. The geometric mean of the reaction time for each condition was calculated. Wrong response times were not included in this mean and neither were excessively short responses (< 100 ms) or excessively long responses (> 1.5 x current mean).

Repetition effect. It is well known that if a subject has to respond to the same condition twice in succession then the second response is faster than the first (Bertelson, 1961; Rabbitt and Vyas, 1973). It was possible to look at this effect in our experiment since two conditions occurred in immediate succession on roughly 12 occasions for each subject. The geometric mean of the reaction time to the first and second of these repeats was calculated. It is clearly of interest to know whether this kind of response facilitation is affected in Parkinson's disease.

Results

Errors. The parkinsonian subjects made more errors than the controls (Mann-Whitney U-test, $z = 1.76$, $P < 0.07$), but the overall error rate was very low (patients = 5 per cent, controls = 2 per cent). Very few reaction times were eliminated either for being too long (patients = 0 per cent, controls = 0.5 per cent) or for being too short (patients = 0.6 per cent, controls = 0.3 per cent) ($F(1,18) = 7.2$, $P < 0.02$).

Reaction times. Groups and conditions were compared using analysis of variance with repeated measures (hand, warning and delay). There was a significant effect of hand so that for both groups the right finger was about 7 per cent faster than the left finger ($F(1,18) = 16.4$, $P < 0.001$). There was a significant interaction between warning and delay so that advance knowledge had a much greater effect prior to a 2000 ms delay than prior to a 250 ms delay ($F(1,18) = 8.9$, $P < 0.01$). There was also an interaction between warning and group so that the control group benefited far more from advance information (19 per cent faster) than the patient group (6 per cent faster). Table 4 shows the mean reaction times for the two groups with and without advance information at the two different delays. It can be seen that with no advance information there is little difference between the two groups. However, with advance information the reaction times of the controls reduced even after the 250 ms delay and dramatically so after the 2000 ms delay. The patient group on the other hand gained very little from the advance information.

Repetition effect. When the subjects had to respond to the same condition twice in succession then the reaction time was about 8 per cent faster on the second occasion. This difference was highly significant ($F(1,18) = 31.9$, $P < 0.0001$) and was the same for both groups.

TABLE 4. THE EFFECT OF PRIOR INFORMATION ON REACTION TIME IN PATIENTS WITH PARKINSON'S DISEASE AND CONTROLS

	250 ms delay				*2000 ms delay*			
	No information		*Information*		*No information*		*Information*	
	Mean	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*	*Mean*	*SEM*
Controls	609	± 21	518	± 28	610	± 24	447	± 28
Patients	623	± 38	600	± 42	611	± 40	565	± 56

DISCUSSION

A major difficulty in comparing and evaluating experiments on Parkinson's disease has been the variation in the stage of the disease and medication of the participating subjects. All patients in this study had unequivocal evidence of Parkinson's disease and in most cases the disease was more severe on the left than the right. In addition, all but 2 patients were taking antiparkinsonian therapy at the time of testing. A critical aspect of our results, however, is that the groups differed on one test (reaction time), but not on the other (tracking). Thus our patients were at a sufficiently severe stage to show an unequivocal impairment without being so generally impaired that the results ceased to be informative.

It is possible that the differences we observed between the two tasks lies, not in the nature of the tasks, but in the fact that different systems were used, that is, finger movements in the reaction time task and wrist and arm movements in the tracking task. However, there is little clinical evidence that the symptoms of Parkinson's disease are so system specific. Furthermore, as will be discussed in more detail below, Evarts *et al.* (1981) observed the same effects in reaction time using a wrist rotation response.

The effects of the track parameters on lag shown in the figure are very similar to those found by Young (1962) for eye movements. There is a steady increase in lag for the unpredictable tracks while lag for the predictable tracks remains close to zero except for the highest frequency. This implies that the breakdown in the tracking response occurred at about 1 Hz. This is somewhat lower than Young observed with eye movements. This might be a consequence either of studying hand movements or of the properties of the joystick with which subjects had to indicate their responses. In Flowers (1978*a*) the tracking of a single sine wave with a joystick also broke down between 1.0 and 1.5 Hz. The relationship between lag and frequency for the unpredictable tracks is fitted very well by a curve based on a constant 130 ms lag between target and subject movement. This relationship breaks down only at the highest frequency just as it does for the predictable tracks.

The most striking aspect of these tracking results is the lack of difference between the parkinsonian patients and the controls. This implies not only that the speed of responding to visual feedback is the same in both groups, but also that the parkinsonian patients have no difficulty in making use of predictable target movements to emit preprogrammed hand movements which anticipate the movements of the target. At first sight our result seems flatly to contradict those of Flowers (1978*a*, *b*), but a more detailed consideration will show that this is not the case. In Flowers (1978*a*), subjects tracked a target moving sinusoidally at similar frequencies to those used in the present study. The parkinsonian patients performed worse than the controls at all frequencies in terms of lag. Like the controls, however, their lag was less for these tracks than it was for 'noise' (i.e. unpredictable) tracks, although the facilitation was not as great. Thus as in our study, the parkinsonian patients were able to gain some advantage from target predictability. The major difference between Flowers' track and ours is that his target moved in one dimension (i.e. left to right to left, etc.) across the screen, whereas our target moved in two dimensions (e.g. in a circle in the case of the predictable tracks). This difference draws to our attention a fundamental problem in the analysis of motor skills, that is, how to segment a movement sequence into its basic elements or units. A likely point for segmentation in Flowers' task would be the end of each sweep at which point a subject has to reverse his direction of movement. In our predictable tracks, in which the target moved in a circle, there is no obvious segmentation point. In line with theories about the control of action (Shallice, 1972; Mandler, 1975) we would assume that at each segmentation point a new unit of movement is initiated. Once initiated, control of these movement units is largely automatic (i.e. not requiring attention) and ballistic (i.e. not involving visual feedback). At the end of the unit or if an error is detected, a new movement unit is initiated. In contrast to the control of the movements the initiations are examples of strategic processing (i.e. they require attention) (Schneider and Shiffrin, 1977). The advanced knowledge of how the target is going to move, which is available for the predictable tracks, can facilitate (1) choice of the appropriate movement unit to initiate, (2) the timing of this initiation and (3) the form of the movement unit once it has been initiated. We would suggest that successful performance of our predictable tracking tasks puts little emphasis on the initiation of movement units since the form is circular and therefore the unit may be long (e.g. several revolutions). In addition the first 30 s of tracking were discarded, during which time any difficulty in initiating the movement may have been overcome. On the basis of the reaction time experiment we would expect this initiation difficulty to be overcome within a few seconds. Unfortunately the data collection routine in the tracking program does not permit analysis of performance into units of less than 30 s and so we were unable to check for initiation problems. Performance in the first 30 s as a whole was not impaired in the parkinsonian group. Flowers' tracking tasks put much more emphasis on the initiation of new movement units because of the obvious reversals of movement direction that are required. This is particularly the case in Flowers (1978*b*), in which subjects had to reverse the direction of movement at a time when the target was not visible. The results of our experiment and those of Flowers are therefore compatible if we assume that parkinsonian patients have no difficulty in using prior information to plan in advance the form of a movement, but do have difficulty in using this information to initiate or select a movement, particularly in the absence of an external trigger (e.g. a moving target).

Our results should not be taken to imply that parkinsonian patients have no difficulty with any kind of predictive movement. Our predictable and unpredictable tracks represent the two extremes of possible range of predictability. The circular movements of the predictable target were demonstrated to the subjects in advance of their performing the task and it was clear that they could make the required movements in the absence of any target to follow. Thus the required movements were already in their repertoire. The important result of the experiment was that the patients could make circular movements of the required amplitude and timing even when the target was moving too fast for this to be achieved using visual feedback. If the preprogrammed movements have to be learned because they are not in the subject's repertoire or because repetitions are not obviously present in the movements of the target, then parkinsonian patients may well be impaired. Some unpublished data from Day and Marsden (Marsden, 1982) seem to confirm this idea. These data suggest that normal subjects learn to make use of target predictability even before they are aware of it whereas parkinsonian patients do not. We are currently conducting an experiment to investigate this point.

In Experiment 2 the form of the movement required was of little importance and the emphasis was thus on the selection and initiation of the movements. In this experiment parkinsonian patients clearly failed to gain advantage from prior knowledge of the movement required.

Taken together the results of Experiments 1 and 2 suggest that parkinsonian patients have difficulty in using advance information either to select an appropriate movement or to initiate that movement. However, once the movement has been initiated its form is not totally dependent on visual feedback and can be controlled by prior information about the movement required. This corresponds very much to the clinical picture in which a patient has difficulty precisely in those situations where he knows what he wants to do, but is unable to select and initiate the movement. This is in contrast to his lack of difficulty in responding to an unanticipated event as when he has to catch a ball (Denny-Brown, 1968).

The results of our reaction time experiment are very similar to those of Evarts *et al.* (1981). Although these workers labelled their conditions choice and simple reaction time the conditions were, in fact, very similar to our cued and uncued reactions. Thus in Evarts *et al.*'s 'simple reaction time' condition the subjects could make 1 of 2 possible responses, but were warned 1.8 to 2.5 s in advance in which direction they would have to rotate their wrists. In the 'choice reaction time' condition no such cue was given. The parkinsonian patients were significantly slower than the controls in the 'simple reaction time' (warned) condition. It was expected that they would be even more impaired in the 'choice reaction time' condition, but in fact they were hardly slower than in the 'simple reaction time' condition. As a consequence of this unexpected result Evarts *et al.* concluded that the parkinsonian patients were unimpaired in 'choice reaction time' and did not collect any control data for this condition. The control data reported by them comes from Talland (1965) from traditional reaction time experiments in which subjects pressed keys in response to coloured light signals. In spite of the problems this raises for interpreting Evarts *et al.*'s data, their results are very similar to ours. The parkinsonian patients show much less difference between cued and uncued reaction time (simple *vs* choice) than do the controls with the patients having similar choice reaction times to the controls, but much slower 'simple' reaction times. Evarts *et al.* had interpreted the difference between 'choice' and 'simple' reaction time in terms of speed of information processing. In these terms it would have to be concluded that parkinsonian patients process information much faster than controls since their choice reaction times are so little slower than their 'simple' ones. This seems very unlikely and we would therefore prefer to interpret the data in terms of the effectiveness of the cue which turns the choice reaction time into a simple reaction time. Speed of information processing would be better investigated by comparing, for example, two choices with four choices. The simple reaction time (one choice) situation is qualitatively different from these conditions in that the response can be prepared in advance. As a consequence, virtually no information has to be processed, particularly if there is a 'ready' signal at a fixed interval before the signal to respond. Table 5 shows our data alongside that of Evarts *et al.* and some studies of reaction times in normal subjects in the same age range. There is considerable consistency in these data both in terms of the magnitude of the reaction times and the differences between 'simple' and 'choice' reaction times in spite of the different tasks used.

TABLE 5. 'SIMPLE' AND 'CHOICE' REACTION TIMES OF PARKINSONIAN PATIENTS AND CONTROLS FROM VARIOUS SOURCES

Source	*Age (yrs)*	*Cue for 'simple' RT*	*Imperative signal*	*Interval (s)*	*Response*	*Cued RT 'simple' (ms)*	*Uncued RT 'choice' (ms)*	*Difference (ms)*
Controls								
Rabbitt and Vyas (1982)	61–69	+ or −	A or B	1	Key press	398	521	123
Suci *et al.* (1960)	60–70	Light	Light offset	2, 3 or 4	Speak	400	680	280
Talland (1965)	60–70?	Genuine simple RT	Light onset	1–4	Key press	310	420	110
Present study	43–74	'READY L' or 'READY R'	'GO LEFT' or 'GO RIGHT'	2	Finger lift	447	610	163
Patients								
Evarts *et al.* (1981)	41–72	Light	Light onset	1.8–2.5	Wrist rotation	397	458	61
Present study	43–74	'READY L' or 'READY R'	'GO LEFT' or 'GO RIGHT'	2	Finger lift	565	611	46

RT = reaction time.

The abnormality on reaction time shown by the parkinsonian patients could be the consequence of failure to hold the appropriate response 'in store' in the interval between the cue and the signal to respond. The normal repetition effect shown by the parkinsonian patients, however, shows that at least some information about a response can be held 'in store' between one trial and the next so that a repeated response can be made with much greater rapidity.

Further, the experiments of Heilman *et al.* (1976) argue against the idea that there is a defect in nonspecific arousal in parkinsonian patients which could account for the reaction time findings; they showed that there was no difference in improvement between controls and patients when a warning signal preceded the reaction time stimulus by 0.5 s. No choice of response was involved in this paradigm and hence no information other than 'get ready' was present in the warning stimulus.

Hassler (1978) deduced from electrical recording experiments that each site of putamen tissue is able to 'enhance alertness, emotional reaction and intentional action to one outer event'. However, the specific improvement in reaction time with prior information that is lost in parkinsonian patients suggests that the ability to activate selectively a particular motor plan for a given task and suppress all others is also a function of the basal ganglia (Schwab and Zieper, 1965; Buchwald *et al.*, 1975). Buchwald *et al.* in fact suggested that they were involved in high level programming whereby 'information has to be transferred across a period of time before a response is initiated', a situation that exists in our reaction time experiment. If the selected plan can be engaged for long enough then features of the movement (e.g. predictive) which are dependent upon other brain regions can be expressed. A weak activation would clearly mean a difficulty in initiation despite prior knowledge of movement requirements and expose the subject to possible spontaneous loss of motion or 'freezing'. At the early stages of the illness this may only be manifested as a general paucity of spontaneous movement or experimentally as the intermittency (i.e. a marked delay between each unit of movement) described by Draper and Johns (1964), but at the advanced stage may be revealed as a contribution to some forms of the 'on-off' effect. The importance of the basal ganglia in also maintaining a movement sequence that has been initiated is supported by Denny-Brown and Yanagisawa (1976), who concluded that the basal ganglia have 'all the aspects of a clearing house that accumulates samples of prolonged activity and on a competitive basis can facilitate any one and suppress all others'.

The demonstration that patients with Parkinson's disease have the capacity to engage in predictive or open-loop controlled behaviour is consistent with the operation of intact lateral cerebellum which probably controls the discharge of task-related assemblies at optimal times and thus avoids feedback delays which would preclude these types of motor activity (Brooks and Thach, 1981). In accordance with this is the absence of recognized pathology or abnormal biochemistry of the cerebellum in Parkinson's disease. This concept is also supported by electrical recording experiments in monkeys which show that about a quarter of caudate, pallidal and putaminal neurons discharge as early as the association cortex during the foreperiod of a delayed response task (DeLong, 1972). In contrast, cerebellar neurons do not discharge in pronounced fashion at this time (Brooks, 1979). This indicates that the cerebellum has a relatively lower position in the motor hierarchy.

It is well known that parkinsonian patients develop tricks to aid the initiation of walking during 'off' periods such as counting down ('3 2 1 go') or using lines drawn on the floor over which the subject is told to step (Martin, 1967). It is of interest that an external trigger of this kind is a feature of the tracking task although this paradigm was not designed to explore initiation difficulties. In contrast, the studies of Flowers (1978*b*) which required reproducing the path of an absent target did not contain this additional stimulus which we argue would have helped to maintain the requisite motor plan activated. The importance of visual information to assist movement in Parkinson's disease is well recognized (Cooke *et al.*, 1978). Denny-Brown (1968) noted that for paradoxical kinesia 'in most instances the special stimulus is visual as when a patient is unexpectedly thrown a ball and succeeds in catching it'. If this is considered in conjunction with our experimental data we conclude that the integrity of the basal ganglia is particularly important for selecting and maintaining motor plans which precede the 'less automatic' movement schedules that characterize voluntary movements rather than the 'triggered' responses such as catching a ball, or tracking a moving target. Further studies of stimuli which release latent motor programs would not only be of theoretical interest but may have important clinical implications.

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A NEUROPHYSIOLOGICAL STUDY OF THE PREMOTOR CORTEX IN THE RHESUS MONKEY

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SUMMARY

The frontal agranular cortex consists of at least three major subdivisions: the precentral motor cortex, the supplementary motor cortex, and the premotor cortex. Of these, the premotor cortex is by far the least intensively studied by neurophysiological methods in spite of recent evidence that it is important in higher order aspects of the cerebral control of movement (Moll and Kuypers, 1977; Roland *et al.*, 1980*b*; Halsband and Passingham, 1982). We have accordingly studied neuronal activity in the premotor cortex of Rhesus macaques operantly conditioned to perform a visually guided motor task. We have concluded that many premotor cortex neurons appear to reflect motor set. Further, these and other premotor cortex neurons show activity patterns during and before the execution of an abstractly guided movement that are strikingly similar to what has been observed in association with movements made directly to visuospatial targets. Finally, a functional relationship of some premotor cortex unit activity to the execution of voluntary movement is supported by its close temporal correlation with the onset of movement, a significant correlation with the acceleration of the limb in some cases, and a uniform specificity for movement execution rather than the visuospatial cues that guide the movement.

INTRODUCTION

The division of the precentral gyrus into a premotor cortex and a precentral (or primary) motor cortex dates from the beginning of this century. Campbell (1905) originally proposed the existence of an 'intermediate precentral zone' immediately rostral to the precentral motor cortex and thought that this cortical field corresponded to the site of Hughlings Jackson's third or highest level of motor organization. Later, Fulton and his collaborators (Fulton, 1934, 1935; Jacobsen, 1934; Kennard *et al.*, 1934; Bieber and Fulton, 1938) supported the idea that the precentral gyrus consists of two functionally distinct motor cortical fields: a precentral motor cortex and a premotor cortex. These ideas were disputed, however, first by Walshe (1935) and Foerster (1936) and later by Woolsey and his associates (Woolsey *et al.*, 1952; Travis, 1955) who denied that the premotor cortex played any role in the cerebral control of movement.

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Recent investigations with electrophysiological techniques have begun to clarify some of the problems regarding the premotor cortex. The premotor cortex appears to be a distinct cortical field within the frontal agranular cortex; it can be distinguished from the precentral motor cortex by its higher threshold for production of intracortical microstimulation effects (Weinrich and Wise, 1982; Sessle and Wiesendanger, 1982), its quantifiably different cytoarchitecture (Weinrich and Wise, 1982), and substantial differences in its connectivity (Hartmann-von Monakow *et al.*, 1979; Muakkassa and Strick, 1979; Sessle and Wiesendanger, 1982). In accord with a postulated role in the control of movement, the premotor cortex contains neurons that often show striking temporal relationships between their activity and movement (Kubota and Hamada, 1978; Godschalk *et al.*, 1981; Rizzolatti *et al.*, 1981*c*; Weinrich and Wise, 1982). Further, many premotor cortex neurons show activity related to sensory signals that guide movements or to the animal's motor set (Godschalk *et al.*, 1981; Rizzolatti *et al.*, 1981*a*, *b*, *c*; Weinrich and Wise, 1982). Observations such as these support a role for the premotor cortex in the sensory guidance of movement.

In the present study, we have focused on three of several unresolved questions. Does the activity of premotor cortex neurons depend on the level of abstraction of the visual stimuli that guide a movement, differ when physically identical cues signal the withholding rather than execution of a movement, or reflect the parameters of active movement? To answer these questions it was necessary to study neuronal activity during continuously monitored limb movements whose magnitude and direction were signalled by a visual display that was physically separated from the target of the limb movement.

METHODS

Behavioural Task

Two male Rhesus macaques (*Macaca mulatta*) were operantly conditioned to perform a visually guided forearm flexion-extension task. The monkeys sat in a primate chair with their left forearms enclosed in a 600 g plastic brace which supported their arms. The brace allowed 45 deg of free motion around the elbow joint in the horizontal plane. A potentiometer coupled to the brace measured limb position. An accelerometer (Endevco 2275) mounted underneath the brace measured tangential acceleration of the forearm and its signal was filtered with a bandpass of 0.1 to 15 Hz. Two spots of light were projected onto a translucent tangent screen 57 cm in front of the animals. The screen subtended 48 deg of the animals' visual space; the screen and animals were enclosed in a completely dark room. The monkeys were conditioned to align a 'position light' and a 'target light' (*see* fig. 1A). The position light was a 0.6 deg diameter light spot which, *via* a servo-controlled galvanometer, moved horizontally on the tangent screen to reflect limb position. The target light was a 0.3 deg light spot controlled by a PDP 11/03 computer. Both lights had a luminance of 0.07 log lamberts as determined by a photographic light meter (Nikon). Twenty degrees of elbow movement produced 30 deg of position spot movement on the visual display. Two experimental conditions were randomly interspersed during the performance of the task: the *movement condition* (fig. 1A–D) and the *no-movement condition* (fig. 1A, E, F). In the movement condition, the monkey aligned the two spots within 2 deg (on the visual display) for 1.3 s (fig. 1A) after which the computer simultaneously changed the location of the target light to one of six randomly chosen target locations (shown in fig. 1A) and brightened it to 0.08 log

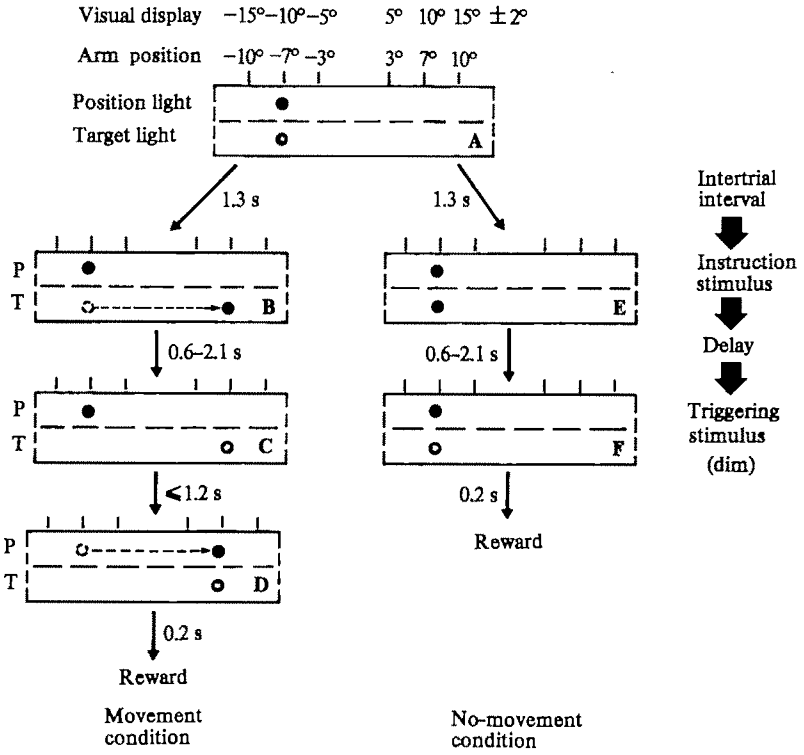

FIG. 1. Diagram of the visual display on the tangent screen during different phases of the behavioural paradigm. The behavioural task is described in Methods. Each rectangle represents the tangent screen at an instant in time. Filled circles indicate fully brightened light spots, stippled circles indicate dimmed light spots, and broken, open circles indicate the immediately preceding location of a light spot. Abbreviations: P = position light spot; T = target light spot. In the example shown here for the movement condition (figs. 1A–D), the monkey is instructed to move the position light spot (coupled to his forearm position through the manipulandum) from −10 deg on the visual display to +10 deg. The monkey (fig. 1D) then executes the 14 deg forearm flexion to realign the position and target lights (a 20 deg movement of the light spot on the visual display). In the no-movement condition (figs. 1A, E, and F), the monkey is instructed to maintain current forearm position.

lamberts luminance (fig. 1B). The change in the target light location served as the *instruction stimulus* (IS). The monkeys were conditioned to withhold response until the target spot dimmed to its original luminance, 0.07 log lamberts (fig. 1C). This degree of dimming was near enough to the detection threshold to require at least approximate foveation. The dimming occurred after one of six randomly chosen delay periods from 0.6 to 2.1 s and served as the *triggering stimulus* (TS). After the triggering stimulus the monkeys were required to realign the position and targets within 1.2 s (fig. 1D). Overshoots were allowed, but the monkeys received a juice reward only if their forearm position light was within 2 deg of the target light 200 ms after they acquired the new target location. If the monkey failed to remain within 2 deg of his initial location during the delay period, the target light was returned immediately to the original location for that trial and then, after the monkey realigned the target and position lights, another target and delay period were randomly selected. If the monkey failed to achieve either the required speed or accuracy of movement, then the behavioural sequence continued unchanged, although the animal did not receive a reward for that trial.

The no-movement condition occurred in one-sixth of the trials, randomly interspersed with the movement condition. In these trials, the target light brightened without changing location (fig. 1E). After a randomly varied delay period, the light dimmed (fig. 1F). The visuospatial cues delivered to the monkey were identical in the two conditions except that, in the no-movement condition trials, the instruction and 'triggering' stimuli required no movement. If the monkey's position light remained within 2 deg of the target location for 200 ms, the monkey was rewarded.

Physiological Recording

After the monkeys achieved reliable task performance, a partial craniotomy was performed under pentobarbitone anaesthesia and a stainless steel recording chamber and head fixation bolts were implanted. The chamber was placed over the right hemisphere, contralateral to the arm that the monkeys used to perform the task. The animal performed the task with his head fixed and directed toward the tangent screen (0 deg in fig. 1A). Single units were isolated with glass-insulated platinum-iridium electrodes (1–3 MΩ at 1 kHz) advanced through the dura mater into the cortex by a hydraulic microdrive while the animal performed the behavioural task. Conventional criteria for unit isolation were employed, and discriminated unit spikes were recorded by a PDP 11/03 computer. The computer also digitized the position and acceleration of the animals' forearms at 100 samples/s and recorded the occurrence of events in the behavioural paradigm. Onset of movement was detected by the computer with a level detector set for small accelerations. In a majority of electrode penetrations, intracortical microstimulation was performed as described previously (Weinrich and Wise, 1982). Daily recording sessions lasted 2 to 3 h.

Silver-silver chloride electro-oculographic (EOG) electrodes were implanted in the temporal bones for recording eye position. Saccades were detected by differentiation and window discrimination of the EOG signal. Eye position was monitored in both monkeys until the electrodes degenerated, after which an a.c. coupled EOG signal was used to detect saccade occurrence and direction. Saccades were also recorded on-line by the computer.

EMG recordings were obtained from a large sample of muscles in sessions scattered throughout the single unit recording sessions. Tungsten and stainless steel electrodes were used. EMG signals were either discriminated and stored in the same manner as the spike data or were rectified and integrated with a resettable integrator (10 ms time constant) (Malmstadt *et al.*, 1974). Muscles monitored, most bilaterally, included triceps and biceps brachii, rhomboid, trapezius, cervical and lumbar paravertebral, extensor carpi radialis and ulnaris, deltoid, brachialis, brachioradialis, supra- and infraspinatus, latissimus dorsi, first dorsal interosseus, sternomastoid, flexor carpi radialis and ulnaris, external oblique, teres major, and gluteus maximus.

Data Analysis

Single units were isolated while the monkey performed the task described above. Every isolated neuron that showed noticeable activity modulation during the execution of the task was studied. Single units were classified on the basis of their activity as displayed in peri-event time histograms. Histograms were constructed to examine activity in relation to the instruction stimulus, triggering stimulus, onset of movement, and saccades for all units. Separate histograms were constructed for each direction of movement. For selected units (approximately half the sample), rasters were constructed in which trials were ordered according to the amplitude of the movement, peak acceleration that occurred during the movement, and the reaction time (defined as the interval between the triggering stimulus and movement onset). Units were also analysed with respect to their activity prior to movement to each target position. Premotor cortex unit activity was classified as signal-, set-, or movement-related. An example of each pattern of activity is shown in fig. 2. Signal-related cells, that is, neurons showing the signal-related pattern of activity, show a transient change in activity following and synchronized with the instruction stimulus. Set-related neurons also show a modulation in activity following the instruction, but that activity is sustained until approximately the time the triggering stimulus occurs. Movement-related cells change activity in temporal relation with the onset of movement. A cell was classified as movement-related if its activity satisfied this definition for some movements, even if it was unrelated to other movements. In each case, the activity associated with the behavioural events was compared to the immediately preceding 1 to 2 s and a change of at least 10 impulses/s was required to classify a neuron as related to a behavioural event. The activity during the intertrial interval was ignored in the present analysis, except as a basis for comparison with event-related activity.

Histological Analysis

The brain was fixed by perfusion with 10 per cent formol-saline while pins were inserted at five known electrode coordinates. The brains were removed from the skull, photographed, sectioned on a freezing microtome at 30 μm in the frontal plane, and stained with thionin. Histological analysis included identification of electrolytic lesions (20 μA for 15 s) distributed throughout the explored region, and was otherwise as described previously (Weinrich and Wise, 1982).

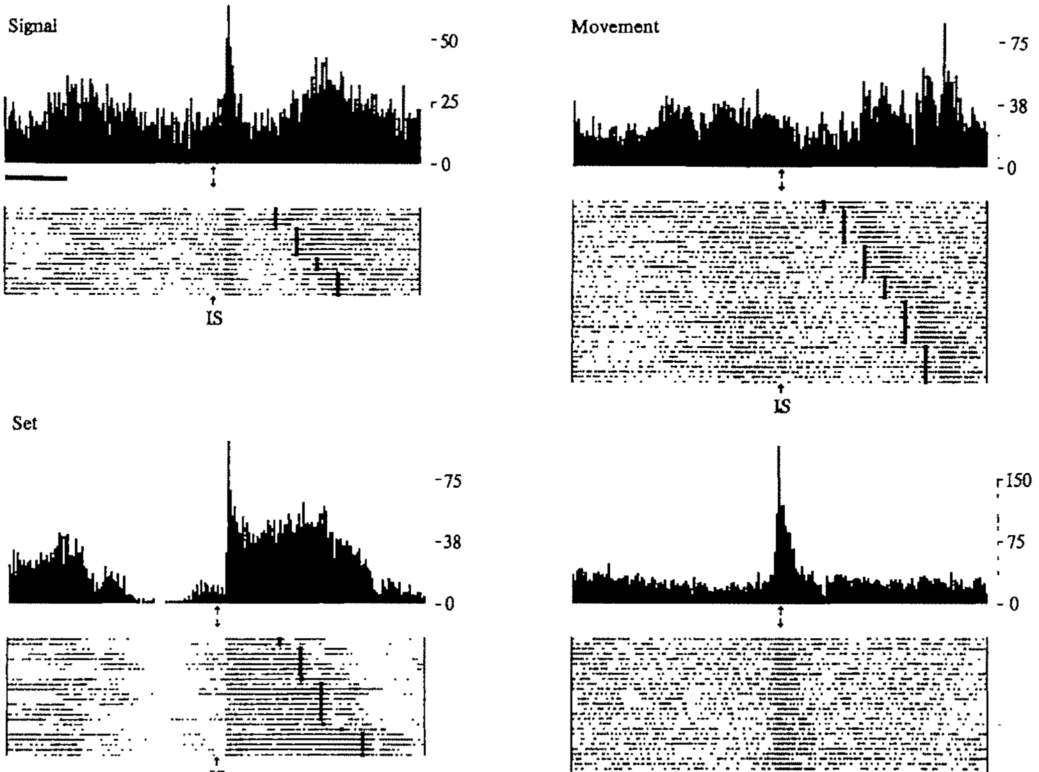

FIG. 2. Example of each cell class as displayed in peri-event rasters and histograms. These three units were located in premotor cortex. Each row of the raster shows the unit discharge activity at the instant indicated by a dot. In the histogram and raster pairs labelled signal, set, and movement, the trials are aligned and centred on the onset of the instruction stimulus (IS; arrow). In the lower right are displayed the same trials as in the upper right, but the trials are centred on the onset of movement (Mvt). The square in each raster line indicates the time of occurrence of the triggering stimulus. The trials are not displayed in the order in which they occurred; in this and subsequent rasters, the trials are reordered according to the time between the event upon which the raster is aligned and the event marked by the square. The impulse rate scale is in impulses/s; the horizontal bar in the upper left indicates 1 s. Binwidth is 30 ms.

RESULTS

Task Performance

Reaction and movement times were consistent over the entire period of recording for each animal, but reaction times (the time from the triggering stimulus to the onset of movement) were significantly different for the two monkeys: the mean reaction time for the first animal was 418 ± 125 ms, for the second animal 298 ± 32 ms. Movement plus reaction times (the time from triggering stimulus to target acquisition) showed similar variability. The mean movement time for the smallest movement (3.3 deg) was 596 ± 180 ms and 436 ± 97 ms for the first and second animal, respectively. For the largest movement (20 deg) it was 825 ± 104 ms and 568 ± 96 ms. Fig. 3 shows two segments of motor behaviour from the first monkey.

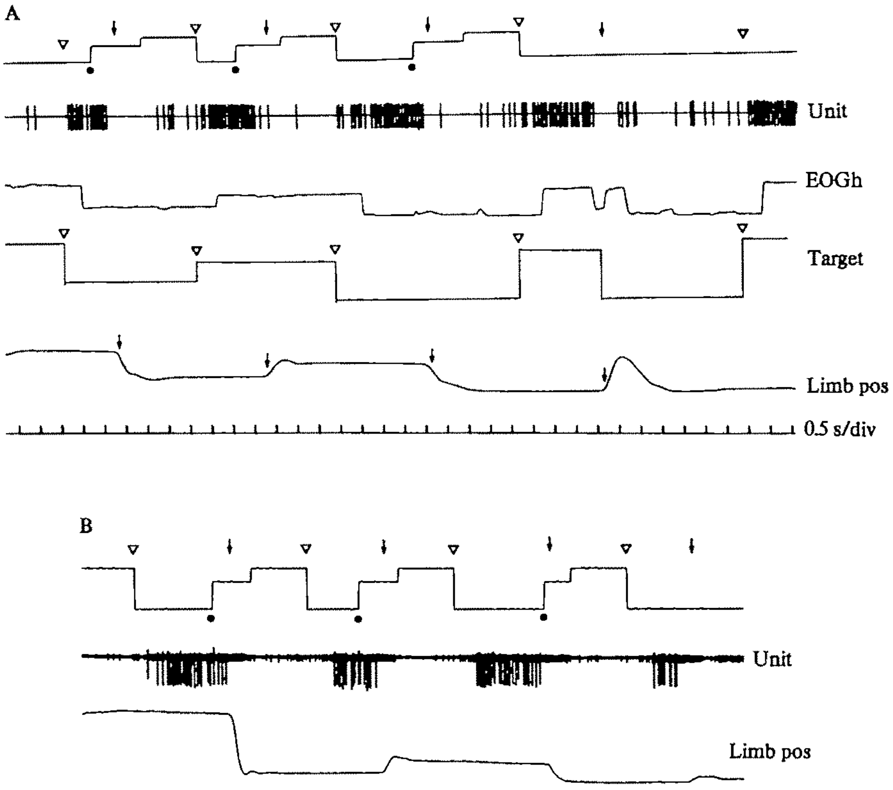

FIG. 3A, record of unit activity, horizontal eye position (EOGh), target position, and forearm (limb) position. Open triangles mark the time of the instruction stimulus, filled circles mark the time of the triggering stimulus, and arrows mark the approximate onset of limb movement. The top trace represents d.c. levels indicating the time of certain events, transition to the highest level indicates the time of reward. Upward movements indicate extensions of the forelimb for the position record and leftward eye movements for the EOGh record. The bottom trace gives the time scale. B, electrode recording of an isolated, set-related unit. Same symbols and time scale as in A.

Both monkeys made accurate movements to the targets. Overshoots were allowed, but could last no longer than 200 ms following the initial target acquisition. In practice, the monkeys rarely overshot the target, doing so on less than 10 per cent of the trials (*see* figs. 7 and 9). However, the monkeys did fail to perform the task correctly on a number of trials, with the number of failures varying, presumably as a function of motivation, from less than 1 per cent of the trials to slightly more than half the trials. Failures took several forms: failure to withhold movement during the delay period; failure to acquire the target within 1.2 s or to remain there for 0.2 s; and, in rare instances, movement in the wrong direction. The trials requiring no movement proved easy for the monkeys; the amount of movement during these trials did not exceed 0.5 deg (*see* figs. 9 and 14). Monkeys depended on the visual cues for performance of the tasks as demonstrated by their inability to perform the task when the position and target lights were switched off.

Muscle Activity

The activity of a variety of muscles was sampled intermittently during the recording sessions (*see* Methods). A sample of EMG activity from the first monkey during both flexion (*left*) and extension (*right*) movements is shown in fig. 4A. In this task a number of muscles show activity changes before or during forearm movement in one or both directions. The pattern of activity shows either a burst of activity before movement, sustained increases, or both. No muscle showed a two-burst pattern that might be expected for the prime mover of a 'ballistic' movement (Angel, 1974). This finding probably reflects the fact that the animals moved the forearms at substantially less than the maximum possible rate. Most muscles became active between 20 and 120 ms before the onset of movement (as determined by a deflection in the acceleration trace), but one, latissimus dorsi in the first monkey, began its change in activity 180 ms before extension movements. Deltoid, rhomboid, wrist extensor and cervical paravertebral muscles were activated in the range of 100 to 140 ms before movement. Muscles in which the activity was correlated with the magnitude of movement were activated 20 to 50 ms before the onset of movement. Brachialis and brachoradialis both show this pattern and timing for flexion movements and show a decrease in activity for extension movement.

We sought to rule out the possibility that transient or sustained neuronal activity during the delay period might be related to startle effects or sustained motor activity rather than motor preparation (fig. 4B). No muscle in either the arm or the thorax demonstrated consistent transient or sustained activity related to the visual cues. No startle effects, that is, transient changes synchronized with a sensory stimulus, were detected in the EMG. There were no EMG changes associated with the no-movement condition. However, one muscle (in the second monkey only), the sternomastoid, appeared to become active when the monkey fixated on targets contralateral to the muscle. The sternomastoid showed this premovement activity on every trial when target was in the contralateral spatial field, regardless of whether the location of the target required a flexion or extension movement. Such a pattern was distinctly different from that of the cells classed here as set-related. Set-related neurons showed premovement activity that either was specific for the direction of upcoming movement (regardless of the location of the target in space) or was constant and directionally nonspecific for all trials. No set-related activity was found for any muscle in the first monkey, although a similar, but quantitatively smaller, pattern was seen for the trapezius muscle in the second animal.

Eye Movements

The appearance of the target light in new positions reliably elicited saccades within 371 ± 101 ms in the first monkey and 259 ± 55 ms in the second. This

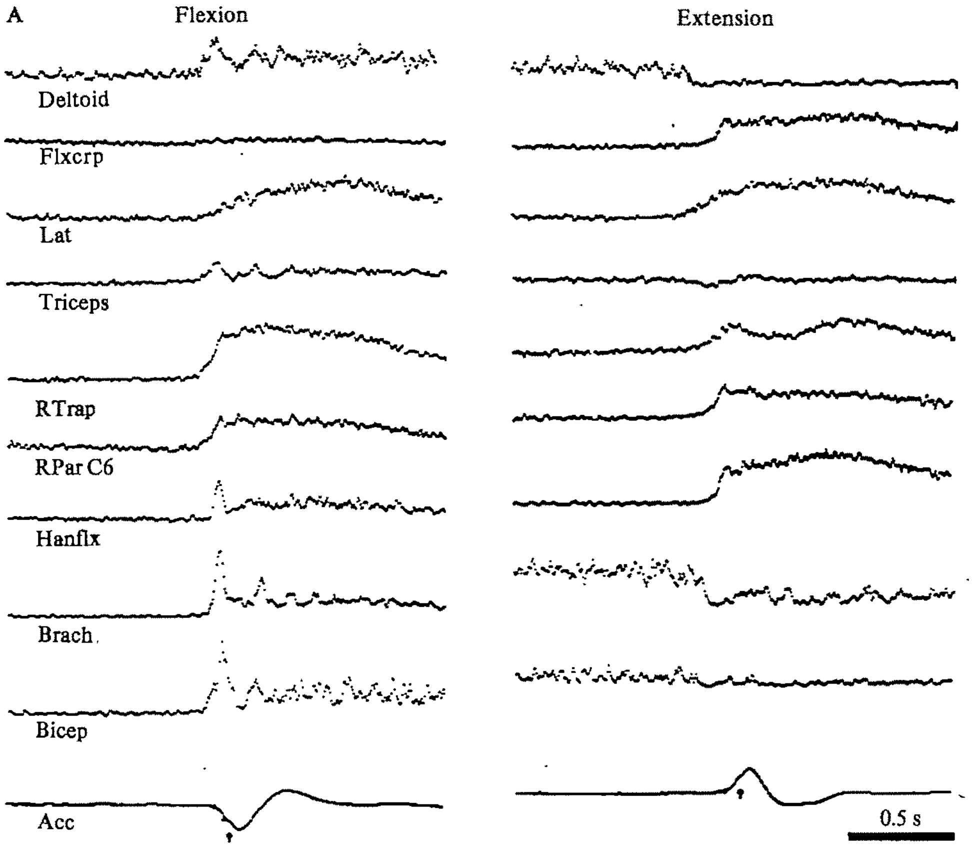

FIG. 4A, EMG activity of selected muscles in the first monkey. Abbreviations: acc = average accleration of the limb; flxcrp = flexor carpi radialis; lat = latissimus dorsi; RTrap = right trapezius; RParC6 = right paravertebral muscles at sixth cervical segment; hanflx = flexor carpi radialis; brach = brachialis; bicep = biceps. All muscles were on the animal's left, except where noted. The arrow marks the approximate onset of deflection in the position trace (not shown). B, EMG of selected muscles during the instructed delay period, i.e. when the monkey withheld movement after the instruction stimulus (IS), but before the triggering stimulus (TS). Abbreviations as in fig. 4A plus: extob = external oblique; flxcrp = flexor carpi ulnaris; extcrp = extensor carpi radialis; tricep = triceps.

difference parallels that seen in the reaction time for arm movements. The second monkey maintained fixation on the target light nearly continuously; the other monkey often made small (< 5 deg) saccades around the target light during the delay period and broke fixation after detecting the target light dim. The difference in reaction time between the two monkeys might largely be accounted for by the shorter time for the second monkey to detect the light jump (since he continuously foveated on the target). Fig. 3 shows a record of horizontal eye position for the first monkey during task performance.

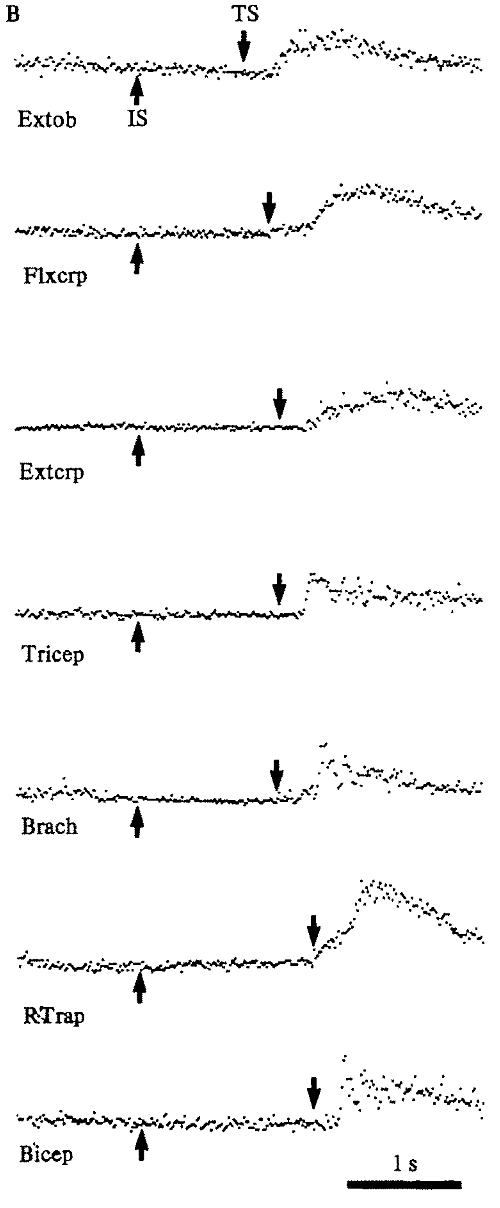

FIG. 4 (*continued*)

Neuronal Activity

A total of 566 neurons were isolated and studied in the frontal agranular cortex, 345 in the first monkey. Neurons were classified, on the basis of peri-event time histograms, as either movement-, set-, or signal-related or as having a combination of these activity patterns (*see* Methods for classification criteria). Their relative proportions are given in Table 1 for each cortical region examined in the present study. The caudal-most region, where microstimulation at a majority (71 of 91) of penetration sites yields a positive microstimulation effect (*see also* Sessle and Wiesendanger, 1982; Weinrich and Wise, 1982). was considered to be the precentral motor cortex. Histological analysis confirmed that this region had a relatively high concentration of large layer V pyramidal cells. Further rostrally was a transition zone about 2 mm in rostrocaudal extent. We considered this zone to be too close to the boundary of the premotor and precentral motor cortex for the units to be assigned unambiguously to either cortical field. Microstimulation effects were inconsistent in this zone and the proportion of large pyramidal cells was substantially less than in the precentral motor region. Whether this transition zone corresponds to a separate cortical

TABLE 1. NEURONAL CLASSIFICATION

Cell class[1,2]	*Precentral*	*Premotor*
Movement	165 (85%)	186 (65%)
Set	28 (14%)	97 (34%)
Signal	30 (15%)	134 (47%)
Total	195	288

[1] Only neurons related to the task are included in this table. Also excluded from this Table are 47 units near the boundary between the premotor and precentral motor cortex and an additional 36 units near the rostral boundary of the premotor cortex. [2] Note that any given neuron can belong to more than one class. Hence, the total for each cortical region may exceed 100 per cent.

field, a functionally distinct part of the precentral motor cortex, or simply results from the inherent inaccuracy in electrode placement is beyond the limitations of our methods. Immediately rostral to this transition zone, units were assigned to the premotor cortex. Microstimulation at these penetration sites rarely (15 of 102 penetrations) evoked movements or muscle twitches at 50 μA.

Several aspects of task-related units will be described below for each activity class: (1) the cortical distribution of each class, (2) the temporal relation of unit activity with the visuospatial cues and active movements, (3) the pattern and magnitude of activity change, including directional selectivity, (4) relationship of unit activity to the parameters of movement and (5) the difference between cell activity in the movement and no-movement condition.

Movement-related units. Movement-related units were distributed throughout the precentral gyrus and postarcuate region, but formed a higher proportion of units in the precentral motor cortex (85 per cent) than in the premotor cortex (72 per cent). Fig. 5B shows the distribution of movement-related cells in one monkey. In this animal, there appear to be two clusters of movement-related cells within the rostral zone considered to be the premotor cortex, on the basis of microstimulation thresholds. One group of cells was located immediately dorsal to the genu of the arcuate sulcus, the other was more dorsal and medial (fig. 5B). In the second monkey (not illustrated, but *see* fig. 5E), there were also two such clusters; one cluster was located immediately dorsal to the arcuate genu, the other directly dorsomedial to the first. The more dorsally situated of the two groups of movement-related neurons in the second monkey (fig. 5B) was rostral to the analogous group in the first monkey.

The latency between the onset of neuronal activity and the onset of movement differed in the premotor and precentral motor cortex. In the premotor cortex unit activity changed at a mean time of 137 ± 61 (SD) ms before onset of movements, whereas in the precentral motor cortex the comparable mean time was 83 ± 57 ms. The median was 150 ms (76 units) in the premotor cortex and 80 ms (93 units) in the precentral motor cortex. These precentral motor cortex and premotor cortex times

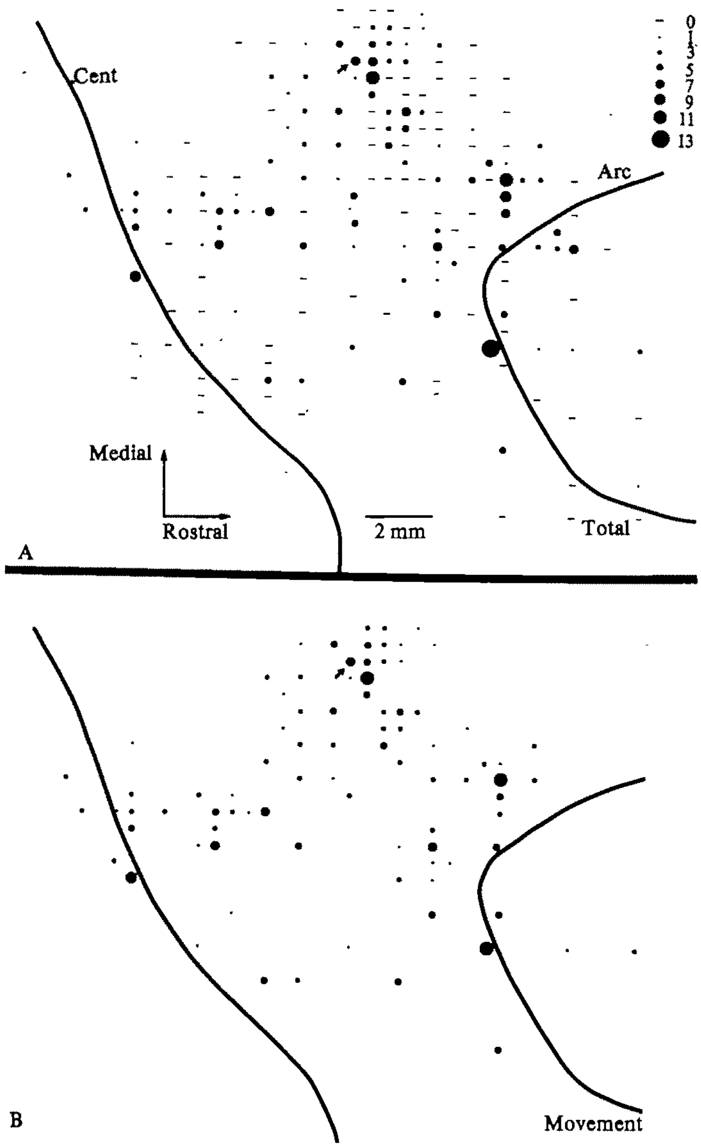

FIG. 5 (*continued overleaf*). Six surface maps of the frontal cortex indicating the location of recording sites and task-related neurons in the two monkeys. A–D are from one monkey, E and F from the other. A, total number of neurons related to the task in the penetration is indicated by the size of the filled circle. The key is in the upper right corner of A. Horizontal lines indicate penetrations in which no related cells were found. B, location and number of movement-related neurons. The number at each site is indicated by the size of the filled circle. C, set-related cell location and number. D, location and number of signal-related neurons. Arrow marks the same penetration in maps A–D and also, for this animal, marks the approximate rostrocaudal level of the premotor cortex/precentral motor cortex boundary as determined by microstimulation methods. E, total number and distribution of task-related units in the second monkey. The distribution of movement-related units, although not shown, was similar to the total distribution of task-related neurons. Same symbols as in A. F, set-related units. Arrows in E and F mark the same penetration. Cent = central sulcus, Arc = arcuate sulcus.

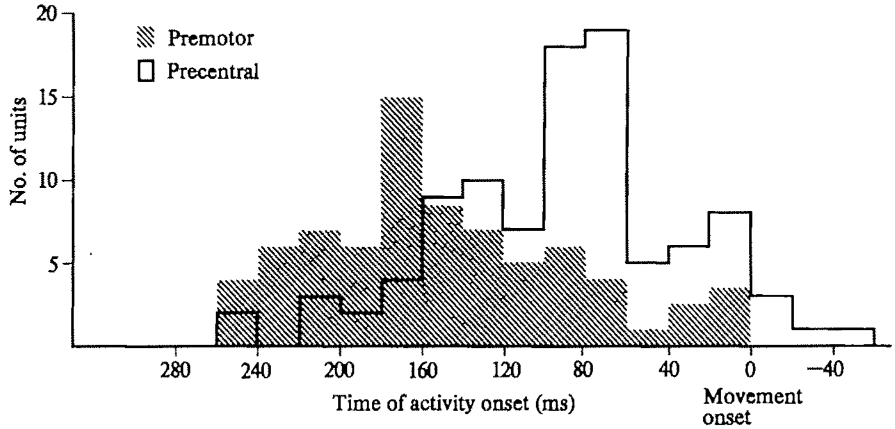

FIG. 6. Distribution of onset times of movement-related unit activity in premotor (hatched histogram) and precentral motor cortex (open histogram). Positive values indicate time before the onset of movement.

direction. Of the directionally selective units, 58 per cent were related to extensions and 42 per cent to flexions. Similar proportions were seen in the precentral motor cortex: 80 per cent (75/94) of the directionally selective cells were unidirectional, 20 per cent reciprocal, and 46 per cent extension-related. Of the nonreciprocal, movement-related cells in premotor cortex 68 per cent (109/160) increased activity and 32 per cent were inhibited in relation to the movement. In the precentral motor cortex, 84 per cent (122/146) of these cells were excited. A sample of 18 movement-related neurons in the premotor cortex and 19 in the precentral motor cortex was selected on the basis of their clear modulation with movements. In the precentral motor cortex these movement-related units showed a mean peak modulation of 74 ± 37 impulses/s and in the premotor cortex, 82 ± 40 impulses/s. The highest peak modulations were 180 impulses/s for precentral motor cortex and 185 impulses/s for premotor cortex.

Movement-related premotor cortex units were examined for relationships between the parameters of movement and neuronal activity. Premotor cortex neuronal activity did not bear any obvious relationship to maintained position of

TABLE 2. DIRECTIONAL SELECTIVITY

	Precentral motor cortex		*Premotor cortex*	
Cell class	*Directional*	*Bidirectional*	*Directional*	*Bidirectional*
Movement	94 (57%)	71 (43%)	91 (49%)	95 (51%)
Set	24 (86%)	4 (14%)	50 (52%)	47 (48%)
Signal	15 (75%)	5 (25%)	67 (59%)	46 (41%)

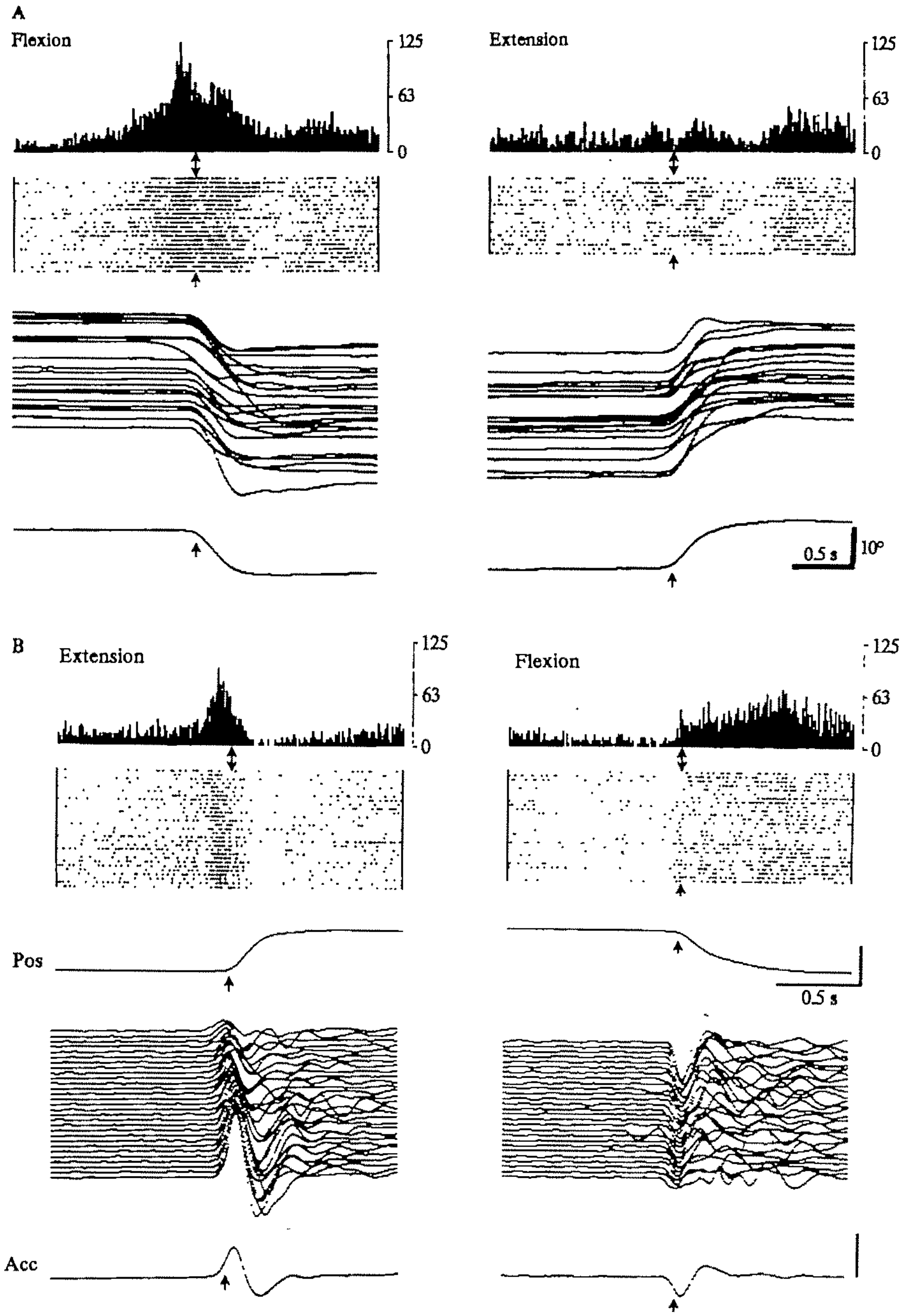

FIG. 7. Two directionally selective movement-related neurons in premotor cortex. A, a unit selective for flexion movements. Below the histogram and raster are the position traces for each individual trial. The bottom trace in each column is the average movement for those trials. Binwidth is 15 ms. B, extension selective unit. Beneath histogram and raster are, in order, the average position trace for those trials, each individual acceleration record (reordered according to peak acceleration) and the average acceleration. The unit activity raster has been reordered in the same sequence as the acceleration traces so that the top line of the raster represents the unit activity for the movement shown in the top line of the acceleration record. Abbreviations: Pos = position of forearm; Acc = acceleration. Binwidth 10 ms. Calibration bars: 10 deg for position; 1000 deg/s^2 for acceleration.

the limb or the target of the movement, that is, units did *not* show a characteristic pattern of activity for movements to a given target regardless of the starting position of the movement, nor did they show different steady-state levels of discharge for different maintained positions. In the latter regard these premotor cortex cells differ from the properties of cells in the precentral motor cortex, and from many task related muscles (not illustrated). A small number of cells showed greater activity preceding movements of greater peak acceleration. Of 25 movement-related cells in premotor cortex examined for such a relationship, 7 of 25 (28 per cent) showed greater activity during movements with greater acceleration. Fig. 8 shows one of these units. Of 33 precentral motor cortex units, 16 (48 per cent) showed such a relationship. The best correlation, in the premotor cortex, between the number of neuronal discharges during the immediate premovement period and peak acceleration was r = 0.68 ($P < 0.001$, n = 38). This correlation is in general agreement with those reported by Kubota and Hamada (1978).

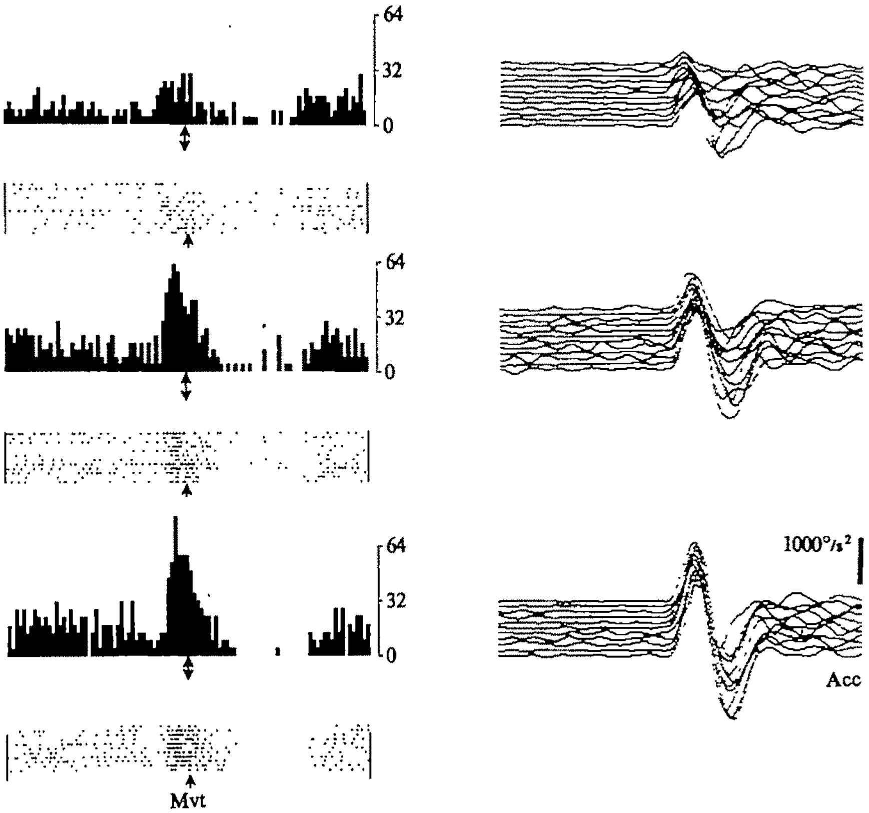

FIG. 8. Three raster and histogram displays for the same premotor cortex unit aligned on the onset of movement (Mvt). The top histogram and raster, and the acceleration traces to the right, are for the movements with the lowest peak accelerations. The raster and acceleration traces are in the same order. The middle histogram and raster pair show the trials with intermediate peak accelerations and the bottom set of records are the trials with highest peak acceleration. The width of each display represents 2 s; binwidth is 20 ms.

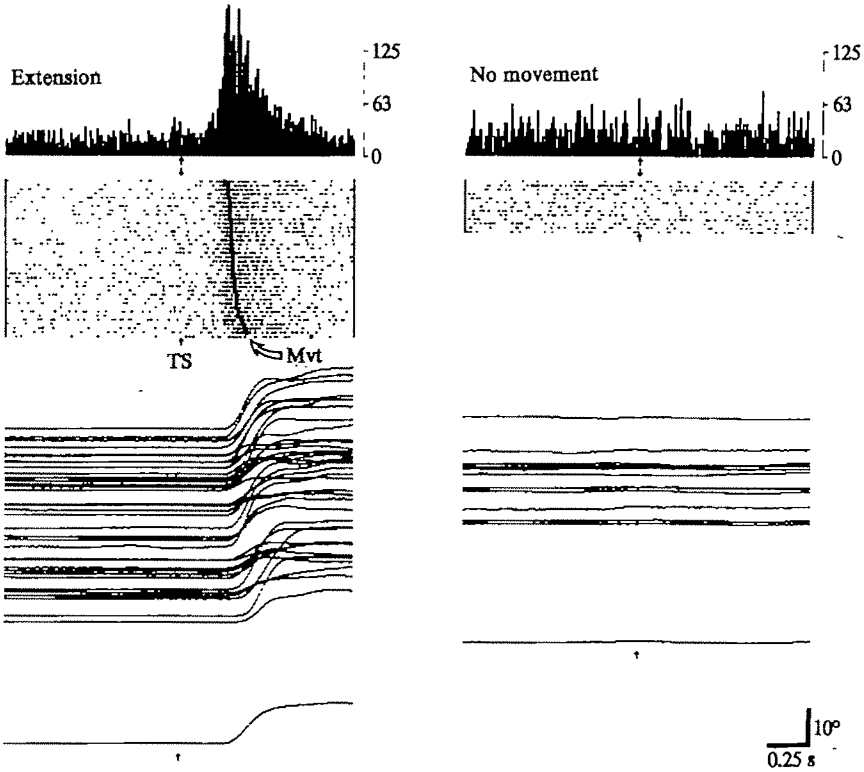

FIG. 9. Movement specificity of movement-related premotor cortex neurons. *Left*, extension trials in the movement condition. The display is aligned on the onset of the triggering stimulus (TS); the square on each raster line indicates the time of the onset of movement (Mvt). Below the raster, the trial-by-trial position record and the average (bottom) are shown. *Right*, same unit during the no-movement condition. The trials are aligned on the presentation of the triggering stimulus (dimming of the target), although in these trials no movement was triggered. Beneath the raster is each position trace and its average. Binwidth is 10 ms.

No neuronal modulations were observed during rewarded no-movement trials for any movement-related unit (*see, for example,* fig. 9). This finding is strong support for the conclusion that the activity is truly related to movement rather than to the visuospatial cues. Furthermore, the variation in the animals' reaction time often provided for a simple demonstration of a closer correlation of unit activity modulation with the onset of movement than with the triggering stimulus (*see* fig. 6 of Weinrich and Wise, 1982). No units were related to the triggering stimulus more closely than to the timing of active movement.

Signal-related units. Signal-related units show a transient change in activity following the instruction stimulus (fig. 2). These cells are distributed throughout the explored region of cortex, but as shown in Table 1 and fig. 5D they are much more prevalent in premotor cortex than in the precentral motor cortex. Fig. 10 shows the

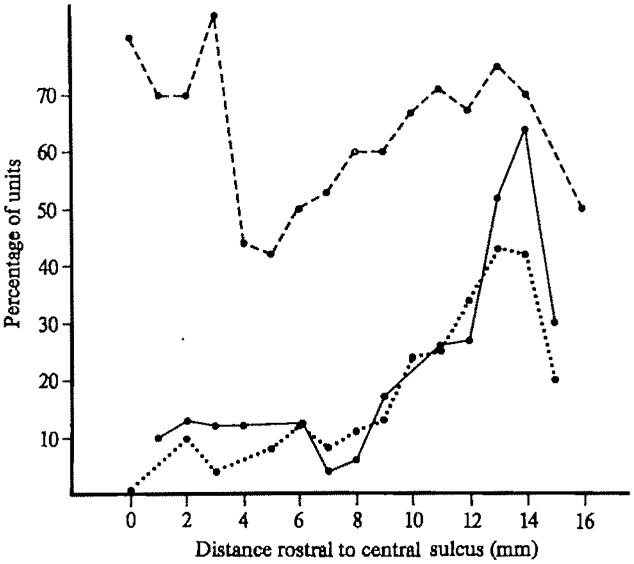

FIG. 10. Proportion of units in each activity class as a function of distance from the central sulcus. Dotted line = set; solid line = signal; dashed line = movement.

proportion of signal-related cells as a function of distance from the central sulcus. The onset latency of signal-related activity is shown in fig. 11A for premotor cortex; the earliest signal-related cell increased discharge 80 ms after the instruction stimulus. A similar range of latencies (80 to 300 ms) was measured in the small precentral motor cortex sample.

Most (62 per cent) signal-related units were directionally selective. That is, they showed modulation when the target jumped to the left or right, but not both (unidirectional cells) or showed reciprocal modulation. Table 2 shows the proportions of the directional and nondirectional units in premotor and precentral motor cortex. Note that this degree of directional selectivity can be considered a lower limit, since the monkeys were not obliged to continue fixation on the target

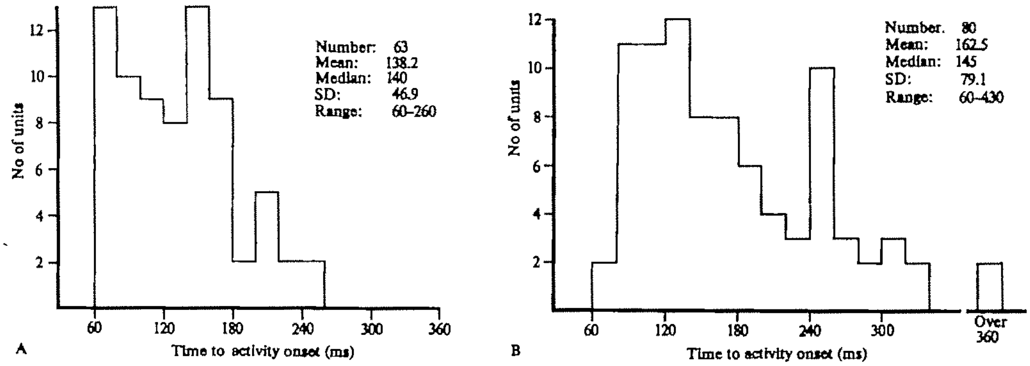

FIG. 11A, distribution of activity onset latencies of signal-related units (the onset of the instruction stimulus is 0 ms). B, distribution of activity onset latencies of set-related units.

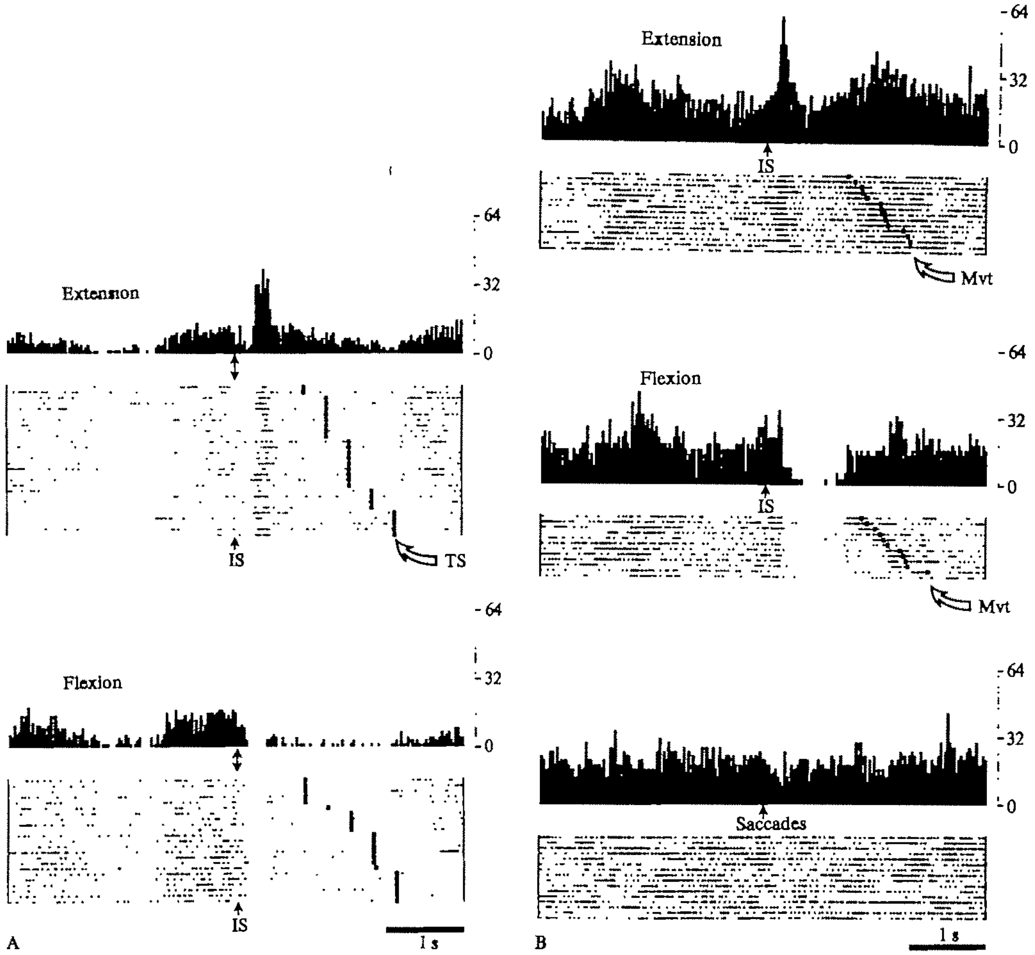

FIG. 12. Directionally selective signal-related neurons in precentral motor cortex (A) and premotor cortex (B). A, unit selectively excited following stimuli instructing extension movements (i.e. target jumps to the left). The raster and histogram are centred on the instruction stimulus (IS), and the square on each raster line indicates the onset time of the triggering stimulus (TS). B, premotor cortex neuron showing signal-related excitation during extension trials (*top raster and histograms*), but not flexion trials (*middle raster*). The square on each of these raster lines indicates the movement onset time (Mvt). The bottom histogram and raster are centred on saccadic eye movements during periods other than immediately after the instruction stimulus (IS). Binwidth is 30 ms.

during the intertrial interval, although they most commonly did so. Fig. 12 shows two directionally specific signal-related cells, one in precentral motor cortex (fig. 12A) and the other in premotor cortex (fig. 12B). Note that the premotor cortex unit (fig. 12B) lacks neuronal modulation in relation to saccades (during the intertrial interval). This lack of a specific relation to eye movements was true of all the cells classed as signal-related and was important to determine since the monkeys' eye movements were closely correlated with the presentation of the instruction stimulus. Most (63/67) of the signal-related premotor cortex cells that showed directional

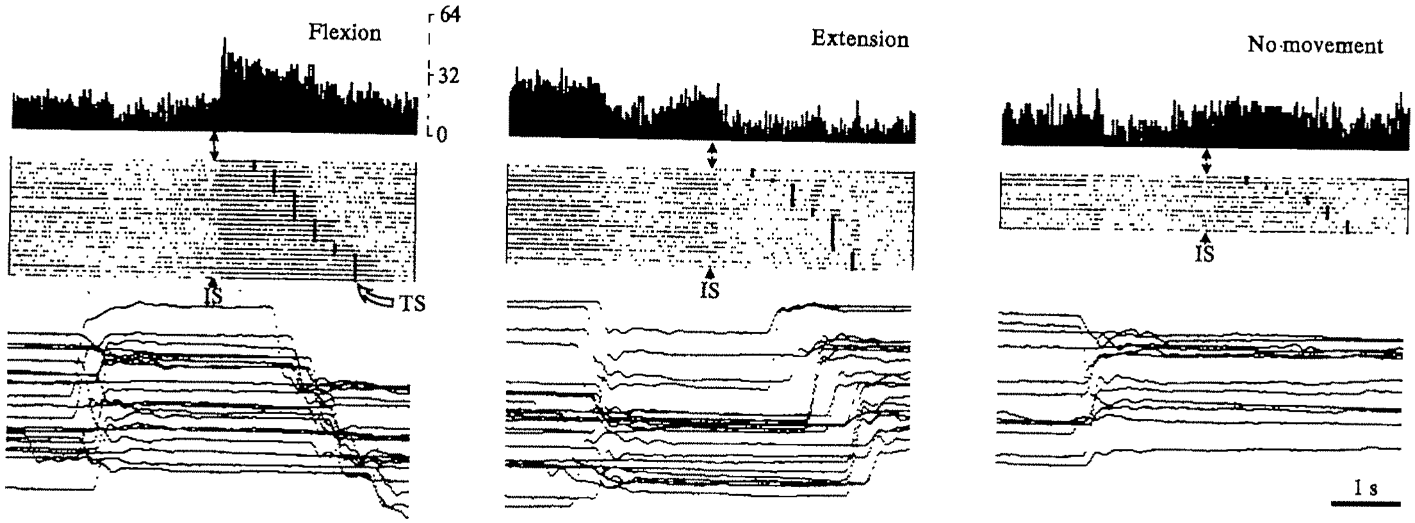

FIG. 14. Premotor cortex set-related unit showing directional selectivity. The unit was excited before flexion movements (*left raster and histogram*), inhibited before extension movements (*middle*), and was without change in activity on trials when the instruction stimulus (IS) signalled no movement (*right*). The square on each raster line marks the time of the triggering stimulus (TS), i.e. the dimming of the target light. Beneath the rasters are the position records for each trial. Binwidth is 30 ms.

flexions. Sixty-two per cent of the unidirectional set-relationships were excitatory and 38 per cent inhibitory. Similar proportions were observed in the smaller precentral motor cortex sample. In a sample of 22 set-related premotor cortex units, the mean sustained set-related modulation was 24 ± 11 impulses/s. The largest modulation was 45 impulses/s. The largest set-related modulation in the precentral motor cortex was 50 impulses/s. The set-related units show no clear selectivity with respect to specific targets.

A striking difference was observed in the set-related activity during the movement and no-movement conditions. This has been reported previously, in preliminary form, for premotor cortex neurons (Wise *et al.*, 1983). We add here the documentation of the lack of movement during the no-movement trials (figs. 9 and 14) and the parallel difference in set-related activity during the movement and no-movement conditions in the precentral motor cortex. Fig. 14 shows the set-related activity of a premotor cortex neuron during several no-movement trials. From a total of 77 premotor cortex neurons, 50 (65 per cent) showed set-related modulation changes (in excess of 10 impulses/s) only during movement trials. Five units showed the converse, activity changes only during the no-movement trials. In the precentral motor cortex, 18 of 23 set-related cells (78 per cent), showed the set-related pattern of activity only when the instruction called for a movement (movement trials). Two additional units there showed activity changes only during the no-movement trials. The mean sustained set-related activity during movement trials of 17.2 ± 10 impulses/s was more than 139 per cent greater than the activity during no-movement trials (7.2 ± 8 impulses/s), a highly statistically significant difference ($P < 0.0001$, $n = 95$; t test, two-tailed).

DISCUSSION

The Role of the Premotor Cortex in Movement

Several proposals concerning the function of premotor cortex dominate the history of its investigation: sensory guidance of movements, control of movement sequencing, preparation for movements, and suppression of primitive (or simple) movement patterns. These ideas have in common the concept of the premotor cortex as a higher level executive controlling the more flexible features of motor behaviour.

Sensory guidance of movements. The concept that the premotor cortex plays a special role in visually guided movements gains support from the responses of its neurons to sensory signals which guide movement (Kubota and Hamada, 1978; Sakai, 1978; Godschalk *et al.*, 1981; Rizzolatti *et al.*, 1981*b*; Weinrich and Wise, 1982). It has been suggested that premotor cortex serves as an integrating centre for visual (and other sensory) information important in the control of movement (Geschwind, 1965; Haaxma and Kuypers, 1975; Moll and Kuypers, 1975). In accord with this idea, Roland and his colleagues (Roland *et al.*, 1980*a*, *b*) in studying cerebral blood flow in humans performing stereotyped motor tasks, found that

WONG Y C, KWAN H C, MACKAY W A, MURPHY J T (1982) Participation of precentral neurons in somatically and visually triggered movements in primates. *Brain Research, Amsterdam,* **247,** 49–56.

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COLOUR ANOMIA RESULTING FROM WEAKENED SHORT-TERM COLOUR MEMORY

A CASE STUDY

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SUMMARY

A patient exhibited marked colour anomia without object anomia, but was able to point to named colours. Five experiments were conducted to investigate his immediate colour memory. It was concluded that his colour anomia was the result of an impaired short-term memory deficit specific to colour. Temporary activation of specific entries in the colour lexicon enabled pointing and even naming to take place. A general model incorporating all forms of colour anomia is presented.

INTRODUCTION

The inability to name visually presented colours is a common result of brain damage especially to the left hemisphere. Colour information can, of course, be coded verbally and/or visually and many investigators have looked at these aspects of the performance of patients with colour related disorders (Geschwind and Fusillo, 1966; De Renzi and Spinnler, 1967; Beauvois, 1982). In most cases, colour anomia is encountered in the setting of a general naming disorder but in a small proportion (around 4 per cent) of such cases, the anomia for colours is quite disproportionate to the anomia for object names (De Renzi and Spinnler, 1967). There is, therefore, a need to postulate neural networks which specifically link colour sensation to a lexicon of colour names. When patients can neither name colours nor point to a named colour, it is reasonable to say that there is a disconnection of these neural networks (Geschwind and Fusillo, 1966) or a functional visual-verbal disconnection (Beauvois, 1982). This combination of symptoms could also be due to a disturbance of the colour lexicon itself (Oxbury *et al.*, 1969) or to an achromatopsia. However, none of these explanations satisfies for cases where pointing to a named colour remains possible when colour naming is severely impaired. Examples of such a dissociation of symptoms can be found in the literature (De Renzi and Spinnler,

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1967; Denckla, 1972; Netley, 1974; Sasanuma, 1974; Basso *et al.*, 1976; Damasio *et al.*, 1979) but are never explained.

It could be argued that pointing to a named colour is an easier task than naming a colour because of the restricted number of alternatives in the former case. This seems unlikely for cases where naming is extremely poor and pointing is perfect. Moreover, it is not uncommon to find patients whose colour naming is superior to their ability to point to a named colour (Goodglass *et al.*, 1966) showing that task difficulty is not necessarily the main determinant of the discrepancy between pointing and naming performance. Another trivial explanation would be a disturbance of expressive speech but this would seem highly unlikely to be specific to colour names. Instead, we propose that colour naming and pointing are mediated by a central lexicon which accepts verbal and visual input. We argue that colour naming is impaired due to a degraded visual input into the lexicon. Pointing is retained because, having been given verbal information, less visual input is required. Thus, when asked to point to the 'red', the entry for red in the lexicon is thereby activated before any visual information is received and less red input is required to elicit the correct response.

MATERIAL AND METHODS

Case History

P.L. is a right-handed male employed as a foreman in a bottling factory. In June 1979 at the age of 47 years he suffered a cerebrovascular lesion. He reported gradual blurring of vision which over a day increased to leave only the left visual field intact. Perimetry confirmed the presence of a right homonymous hemianopia with macular sparing. The visual acuity was 6/6 from each eye uncorrected and there were no motor or sensory signs in the face or limbs. Pupil reflexes were normal. Investigation of the fundi ophthalmoscopically showed normal discs, maculae and vessels except for slight temporal pallor to the left optic disc. There was a history of hypertension. The CT scan (fig. 1) revealed a large well localized infarct in the left occipitotemporal region presumably arising from an occlusion of the left posterior cerebral artery.

Neuropsychological Assessment

The patient was assessed twenty-two months after his stroke. Administration of the Wechsler Adult Intelligence Scale (WAIS) gave a verbal IQ of 108 and a performance IQ of 86. This verbal-performance discrepancy is not due to disproportionally low performance on any subtest (Table 1). A

TABLE 1. DETAILS OF 'WAIS' SUBTESTS (AGE SCALED)

Verbal		*Performance*	
Information	12	Digit symbol	6
Arithmetic	9	Picture completion	9
Similarities	15	Block design	7
Digit span	10	Object assembly	8
Vocabulary	11		
Verbal IQ 108 (prorated)		Performance IQ 86 (prorated)	

similar pattern of performance on the WAIS was given by the patient of Sasanuma (1974) who was right handed and exhibited a similar anomia to P.L.

There was evidence of mild impairment of memory, as assessed by delayed story recall. Initially there was a certain amount of perseveration on the Oldfield-Wingfield Object Naming test but subsequent retesting (concurrent with this study) two and four months later gave virtually error free (35/36) performance. This is in sharp contrast to his colour naming which was poor at first testing and has remained so. At the time of this study there was no evidence of impairment of auditory comprehension, as assessed by the Token test and the Goodglass-Kaplan test. Earlier assessment did suggest a borderline impairment on the Token test. Spontaneous speech and repetition were unimpaired.

Reading and writing were performed only slowly and while still improving were nevertheless carried out in a halting fashion. There were also occasional difficulties with oral spelling and a certain amount of visual confusion among letters.

Colour Vision Testing

Colour perception was tested with both an anomaloscope and the Farnsworth-Munsell Hundred Hue test conducted under artificial daylight (illuminant C). The Farnsworth-Munsell test was performed in the normal time and gave a small anarchic hue discrimination loss (*see* Table 2) without

TABLE 2. COLOUR VISION TESTING ON THE FARNSWORTH-MUNSELL 100 HUE TEST AND ANOMALOSCOPE

Farnsworth-Munsell

	P.L.	*Normal**
Binocular	19.50	8.68 (2.64)
Right eye	22.86	10.36 (2.43)
Left eye	22.07	10.22 (1.99)

* Data from Verriest *et al.* (1982); standard deviations in brackets.

Anomaloscope

	Midmatching point		*Matching range*	
	Aperture		*Aperture*	
Equation	*2°*	*0.5°*	*2°*	*0.5°*
Red/green				
Right eye	28.0	28.0	8.0	18.0
Left eye	30.5	31.0	5.0	14.0
Yellow/blue				
Right eye	30.0	25.0	2.0	30.0
Left eye	21.5	30.0	13.0	30.0

*Normal data (equal for both eyes and apertures)**

	Midmatching point	Matching range
Red/green	25.0 (0.75)	1.8 (1.75)
Yellow/blue	31.0 (4.30)	10.0 (9.00)

* Standard deviations in brackets.

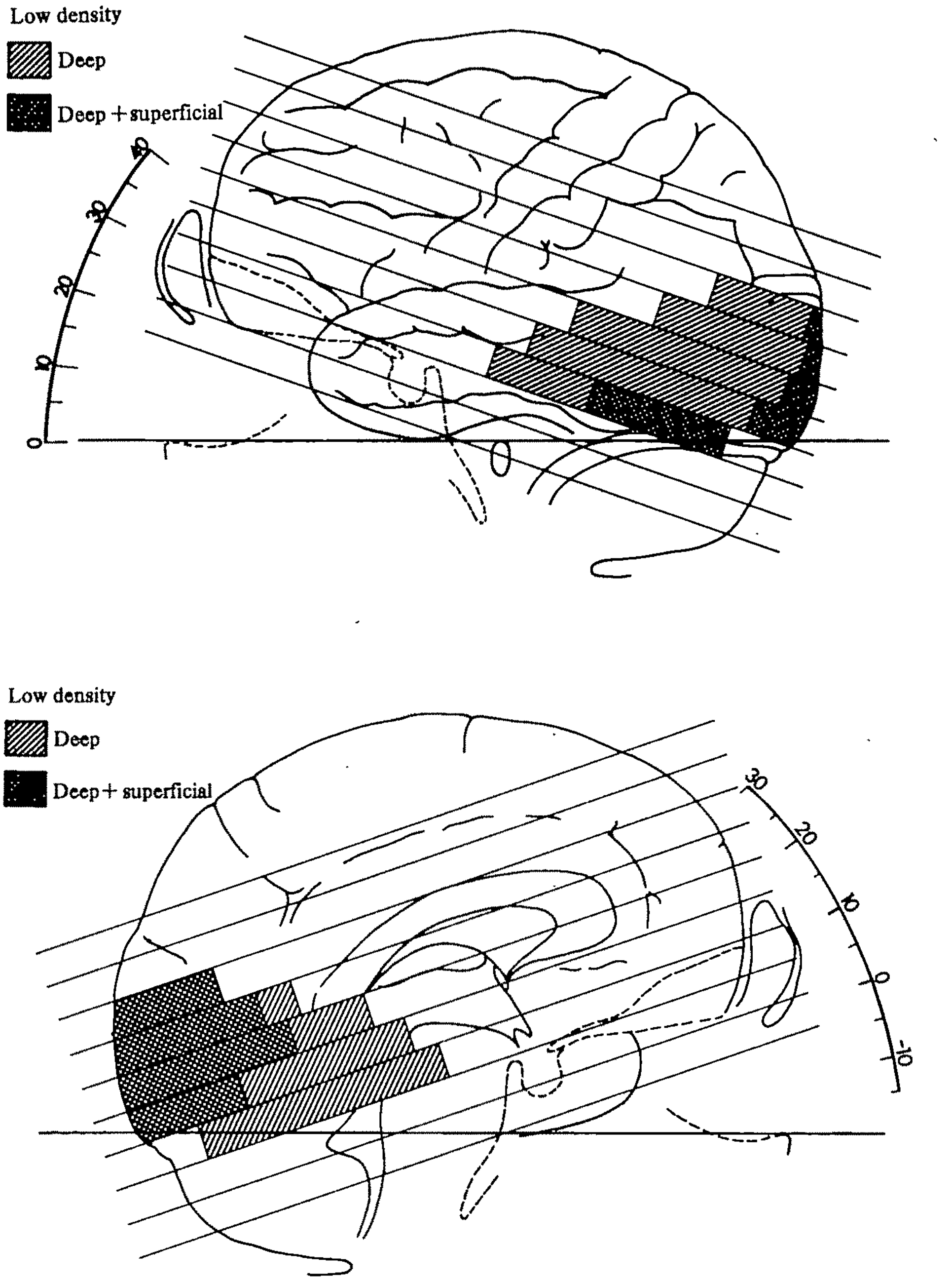
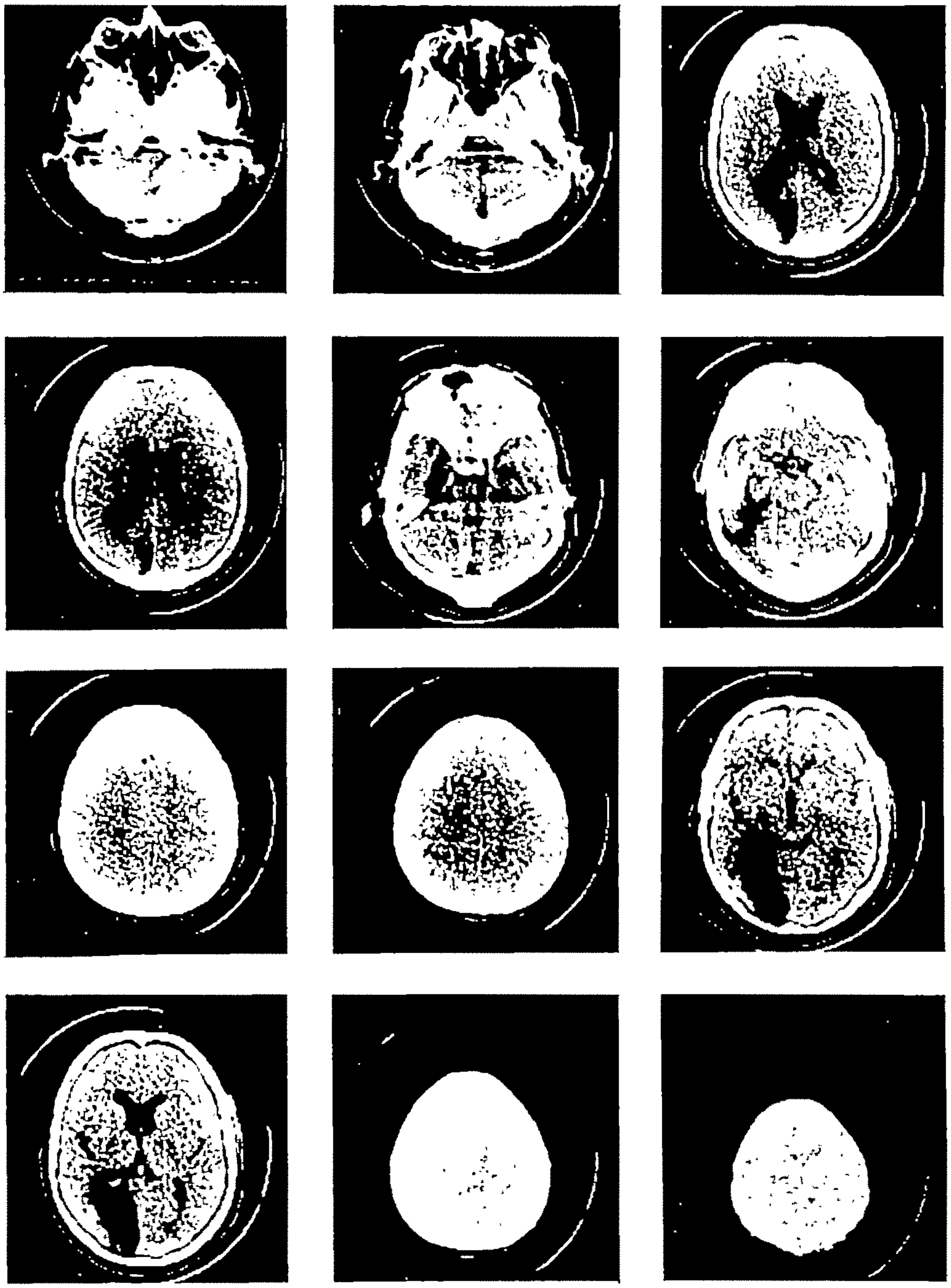


FIG. 1. Map of P.L.'s lesion and CT scans (*opposite*). Mapping was carried out by the procedure described by Mazzocchi and Vignolo (1978).



any clear confusion axes which suggests an acquired rather than a congenital loss. This conclusion was confirmed from testing on the anomaloscope as the range of acceptable matches changed with decreasing aperture size, which reflects a loss for central vision (Table 2). Deviations from the norms of the instrument for both midmatching point and matching range were relatively small (Lakowski, 1971). The patient's colour vision disorder was classified as a mild type II (acquired) defect (Pinckers *et al.*, 1979). The left eye had somewhat greater deviation for the yellow-blue equation midmatching point and matching range; this monocular effect also points to an acquired aetiology. The effect of this colour disturbance is small and typically would not affect the performance with chromatically widely spaced and saturated colours as used in the subsequent tests described below.

Because colour naming was to be tested in detail it was necessary to ensure that colour discrimination was not stretched in any of the tests to be performed. Therefore, colour discrimination was investigated by colour sorting and matching of the colours that were to be used. Presented with 10 examples of each colour in a random order and asked to arrange them in piles, the patient made no errors.

TABLE 3. P.L.'S COLOUR NAMING

Colour presented	*Name given*									
	Red	*Green*	*Yellow*	*Purple*	*Orange*	*Blue*	*Pink*	*Grey*	*Brown*	*Black*
Red	4*	2	3	—	3	2	—	—	1	—
Green	2	7*	2	—	4	—	—	—	—	—
Yellow	1	—	14*	—	—	—	—	—	—	—
Purple	1	—	1	6*	—	4	—	—	2	1
Orange	1	—	5	1	5*	—	—	—	3	—
Blue	1	1	—	—	—	11*	—	—	2	—
Pink	3	—	4	—	6	1	1*	—	—	—
Grey	—	—	—	—	—	—	—	1*	12	2
Brown	1	—	—	—	1	3	—	1	9*	—
Black	—	—	—	—	—	—	—	—	—	15*

* Correct name.

Colour naming and pointing to named colours were tested with 10 colours (*see* Table 3), presented as 1 in. squares on a white background. All 10 colours were always present. Colour naming was very poor but the patient made no errors when asked to point to a named colour or to point to a written colour name. Colour naming has been tested at various times for this patient and Table 3 gives the frequency of alternative colour names for each colour on presentation. It can be seen that this does not correspond to a colour naming deficit caused from a genetic disturbance of colour vision (Kalmus, 1965).

He never corrected himself except when he had just given that colour name to a different patch. For instance, having incorrectly named a green patch red, he would on presentation of a red patch occasionally point out that his last response must have been wrong. Such errors made him aware of his colour naming problem, but this has not helped him. Pointing to named colours was tested on 5 occasions (20 trials each) and no errors were made. He never reported any fluctuation in perceived colour or any other perceptual anomaly.

EXPERIMENTAL OBSERVATIONS

In the early stages poststroke, P.L. did display a mild aphasic disturbance. Experiment 1 was conducted in order to verify that a loss of colour names *per se* was not the cause of the colour anomia. This was tested in a recognition memory task in which either colour names or colour patches were presented. Five items, either spoken colour names or visual colour patches, were presented sequentially at a rate of 1/s. The colour patches were 1 in. squares mounted on white card. The colours were chosen at random from red, yellow, green, blue, black, pink, orange, violet, brown and grey. Following the last presentation, probes of either a coloured patch or a colour name were given and a yes/no decision made as to whether it was one of the original 5. Six such decisions were made to each list. Probes were given in a pseudorandom fashion ensuring that all 4 combinations of modality of presentation for stimulus and probe occurred equally often. P.L. and two controls matched for age, sex, occupation and educational backgrounds were tested. Fig. 2 shows that it is only if both stimulus and probe are colour names that performance is normal. Thus there is no difficulty with colour names *per se* but there is if any aspect of the task involves a visually presented colour. This could be due to either poor visual memory or as a result of storing inaccurate colour names in verbal memory. In order to decide between these alternatives it is necessary to establish whether verbal or visual coding is employed.

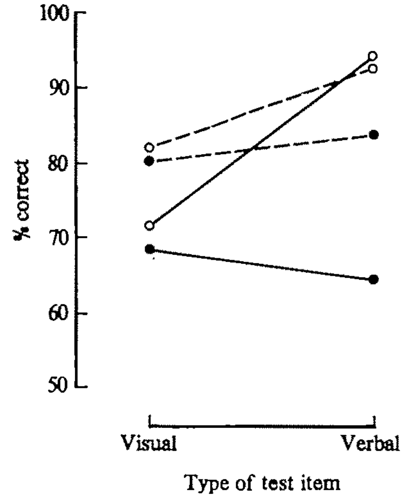


FIG. 2. Recognition memory for sequentially presented colours. The graph shows the performance of P.L. and controls with visual and verbal presentation of stimuli and test items. Chance performance would provide 50 per cent correct. Visual presentation (closed circle). Verbal presentation (open circle). P.L. (solid line). Controls (broken line).

In Experiment 2 we introduced visual or verbal interference in order to establish the mode of encoding. Three coloured patches were presented for 10 s and after a delay of 10 s the subject was required to select the 3 original colours from 10 alternatives. The colours used were the same as in Experiment 1. The delay was unfilled or filled with verbal or nonverbal (colour) interference. The nonverbal interference was matching colours and the verbal interference was counting backwards in threes from a three digit number. Three controls were matched to P.L. for age (within 2 years), sex, profession and educational background. Fig. 3 shows that, for controls, performance is virtually error free in conditions with no

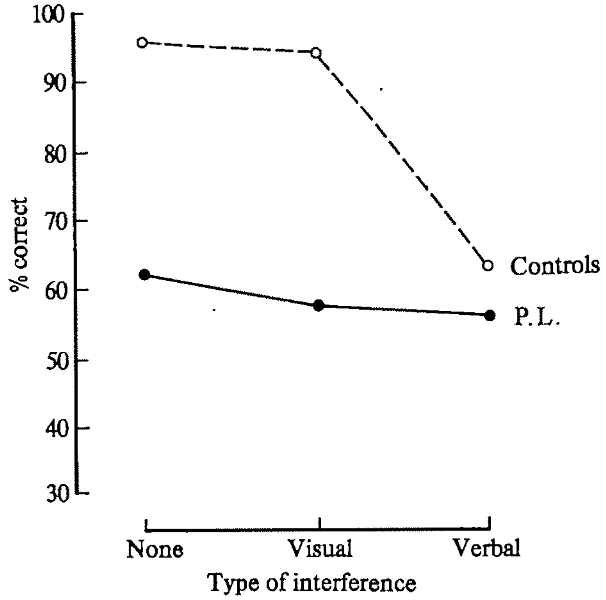


FIG. 3. Recognition memory for 3 simultaneously presented colours after visual, verbal or no interference. Chance performance would be 30 per cent correct.

interference and visual interference but a marked decrement is observed with verbal interference. Thus, for controls, the task involves verbal labelling. P.L. performed just as poorly without interference as with verbal interference. However, it is possible that P.L., like normals, employs verbal coding, but unlike normals, labels the colours incorrectly and commits these wrong labels to memory. If this is the case, verbal interference would affect both correct and incorrect labels leaving the performance level relatively unchanged.

We assessed the extent to which P.L.'s recall was dependent upon labelling by requiring him to name overtly the 3 presented colours in a no interference condition. Fig. 4 shows that overt labelling did not change the overall level of performance and also that when P.L. correctly named a colour he almost invariably recognized it correctly. It can be clearly seen that the vast majority of errors correspond to incorrect labels. Experiment 2, therefore, shows that P.L., like controls, employs verbal coding in this task but, unlike controls, incorrectly translates a visual stimulus into a verbal code.

The next question to consider is why P.L. did not turn to a visual code in Experiment 2, given that his labelling is poor and he is aware of it. The next experiment was designed to determine if P.L. could use visual coding under conditions where verbal labelling would be ineffective. A task based predominantly on visual coding was devised, which involved remembering a coloured patch and, after a variable delay, selecting the colour from 3 alternatives. These 3 choice alternatives were of similar hue and would be given the same colour name. Thus,

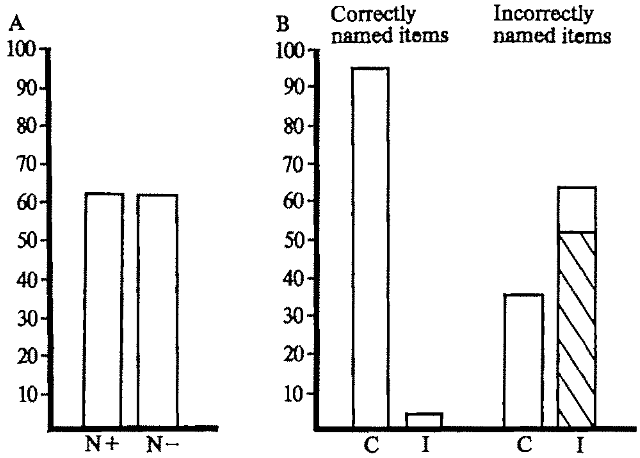


FIG. 4. Recognition memory in relation to overt naming. A shows overall performance with and without overt naming. B shows breakdown of performance in the overt naming condition. A, percentage correct; N+ = with overt naming. N− = without overt naming. B, percentage responses: C = correct recognition memory responses; I = incorrect recognition memory responses. Incorrect recognition memory responses corresponding to incorrect name (hatched area).

simple verbal labelling would not be effective. Over the whole experiment, the range of hues was such that no hue was employed in more than one trial and therefore subjects would not become familiar with individual items, which otherwise might facilitate verbal descriptions. Labelling the item to be remembered in terms of brightness and saturation could, of course, not be done in relation to the test alternatives and is therefore unlikely to be an effective strategy. To verify that these materials would indeed be coded visually, a preliminary experiment was performed with normal control subjects. A single colour patch (3 cm × 1.7 cm on a 9 cm × 6 cm white card) was presented for 5 s and followed after a delay of 4 or 8 s by 3 test items, one of which was identical to the original. The test items (same size as stimulus patch) were arranged on the vertical meridian with 0.5 cm space between horizontal edges and the middle item placed in the centre of the 9 cm × 6 cm white card. The delay interval was unfilled or filled with either verbal or visual interference. The verbal interference was counting backwards in twos, rather than threes as in Experiment 2, because of the need to ensure that a sufficient number of verbal responses was produced during the relatively short delay. Pilot testing with counting backward in threes showed that very few verbal responses were produced during the retention interval and the lack of a verbal interference effect might therefore be attributed to the paucity of verbal responses. The visual interference task was to find the 2 identical colours in a set of 3 for the 4 s delay and in a set of 12 for the 8 s delay. The colours used in the interference task were similar to the colour to be remembered. An analysis of the data in Table 4(A) shows that there is only a significant difference between interference conditions ($F_{2,4} = 20.61$, $P < 0.01$). Pairwise comparisons of the interference conditions revealed that performance with visual interference was significantly inferior to performance with both no interference ($t_2 = 5.36$, $P < 0.02$) and verbal interference ($t_2 = 9.7$, $P < 0.01$). There was no significant difference between the verbal and no interference conditions ($t_2 = 1.99$, n.s.).

TABLE 4. NORMAL SUBJECTS' RECOGNITION MEMORY FOR COLOURS (A) OF SIMILAR HUE AND SIMILAR SHAPES (B), BOTH UNDER THREE INTERFERENCE CONDITIONS (PERCENTAGE VALUES)

	A. Colours		*B. Shapes*	
	Delay in seconds		*Delay in seconds*	
	4	*8*	*4*	*8*
No interference	88	83	91	90
Verbal interference	80	69	82	87
Visual interference	61	48	78	68

Having established that the above procedure requires visual coding, we return to the question of P.L.'s inability to use such a code. P.L. and 6 different controls matched for age, sex and educational background performed Experiment 3 without interference at delays ranging from 0 to 4 s. P.L. was also tested at 5 s delay. The order of occurrence of delays was counterbalanced within blocks of 45 trials. As with all other materials used to test P.L.'s short-term memory it was ensured that he could discriminate perceptually between alternatives. He could sort these colour patches without error and when presented with the stimulus and test alternatives simultaneously he made no errors in detecting the 2 identical colours. This was carefully checked so that any observed memory disorder for the colours could *not* be attributed to impaired colour discrimination. Zero seconds delay in the memory test was achieved by placing the card with the 3 test alternatives on top of the card with the colour to be remembered. The remaining delays were timed with a stopwatch. Reliable and consistently timed delays were achieved by having one experimenter present the stimulus items while a second experimenter timed the interval and presented the choice alternatives at test. Fig. 5A shows the rapid decline in the performance of P.L. relative to controls over this time interval so that already at 4 s he is approaching chance level. However, even at zero delay P.L.'s performance does appear to be slightly inferior to the controls. It could be argued, therefore, that the rapid decay shown by P.L. would also be exhibited by controls if they had started from the same trace strength. To consider this point, 6 further controls were run who performed at approximately the same level as P.L. at zero seconds delay. This was achieved by allowing these subjects only 1 s, instead of 5 s, to examine each stimulus item. In all other respects the procedure was identical to that described above.

An interaction between delay and exposure time (in particular, a shorter exposure time producing a more rapid decay) would suggest that P.L.'s performance could be attributed to his weaker initial trace. A two way analysis of variance with repeated measures on one factor revealed only one significant effect, namely that of exposure time ($F_{1,10} = 34.13$, $P < 0.01$). Delay failed to reach significance ($F_{2,20} = 2.33$, $P > 0.1$), but more importantly the interaction did not approach significance

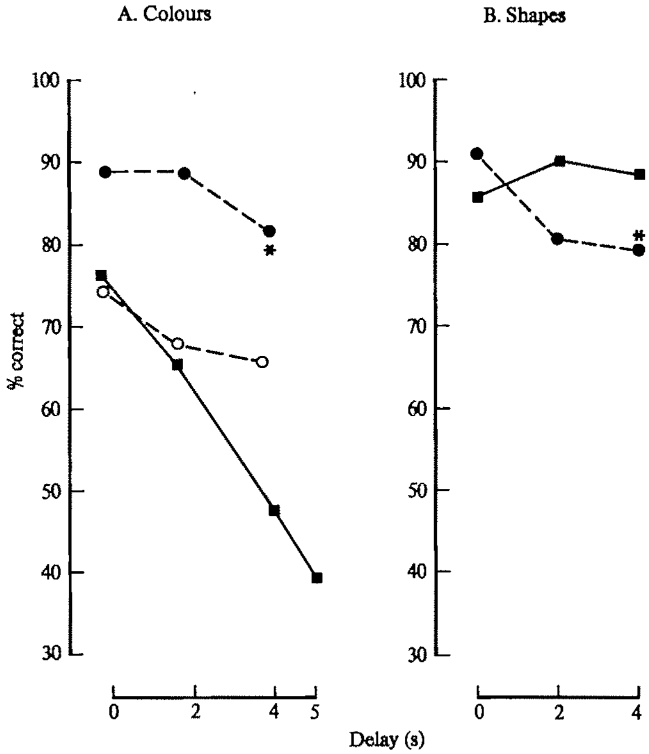


FIG. 5. Recognition memory for colours (A) and shapes (B) in a task not involving a verbal component. Chance level would be one-third correct. P.L. 5 s exposure (■——■). Controls 5 s exposure (●--●). Controls 1 s exposure (o--o). *Controls with verbal interference (*see* Table 4) 5 s exposure.

($F_{2,20} < 1$). We can therefore conclude that the rapid decay shown by P.L. cannot be attributed to his initial trace strength at zero seconds delay.

P.L. therefore has a short-term visual memory deficit for colours and cannot turn to his visual code to perform tasks like Experiments 1 and 2. We cannot, of course, exclude the possibility of a minor verbal component in the present task, but even a comparison between P.L.'s performance with no interference and controls with verbal interference (*see* fig. 5A) does not diminish P.L.'s deficit. Furthermore, we know from Experiments 1 and 2 that P.L. is capable of remembering verbal labels over the time intervals used in this experiment and therefore any impairment in performance due to a labelling deficit should not interact with loss from any other source to produce a more rapid decay. Thus, P.L.'s deficit of short-term memory for colours cannot be attributed to verbal factors.

We can now ask the question whether this is a general visual or specific colour defect of short-term retention. To answer this question an experiment was carried out analagous to Experiment 3, but with complex shapes (fig. 6) rather than colours.

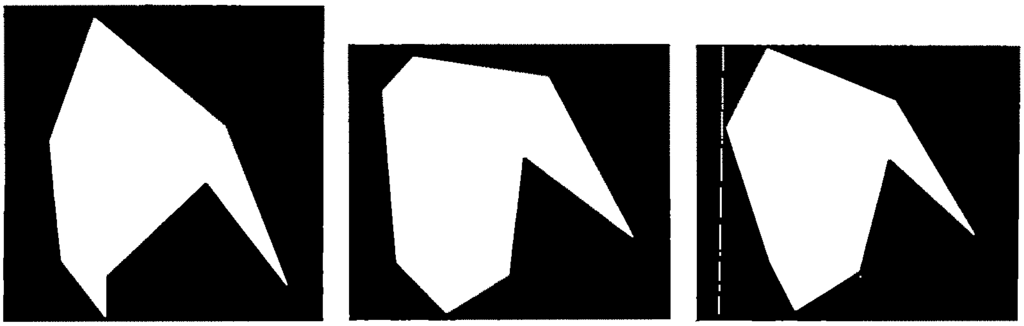


FIG. 6. Meaningless shapes as used in Experiment 4.

As in Experiment 3, it was necessary to show that, for good retention, visual coding of the shape stimuli was required. Controls were therefore tested with no interference, either verbal or visual. The verbal interference task was again counting backwards in twos and the visual interference task was finding 2 identical complex shapes in a set of 3 for the 4 s delay and in a set of 12 for the 8 s delay. An analysis of the data in Table 4(B) shows there is only a significant effect of interference conditions ($F_{2,10} = 7.04$, $P < 0.01$). Pairwise comparisons of the interference conditions revealed that performance with visual interference was significantly inferior to performance with no interference ($t_5 = 3.32$, $P < 0.05$) and verbal interference ($t_5 = 3.79$, $P < 0.02$). There was no significant difference between verbal and no interference conditions ($t_5 = 1.09$). Therefore, the shapes, just like the colours, predominantly require visual coding.

P.L. and 3 matched control subjects were tested in the shape memory task with delays of 0, 2 and 4 s without interference. Fig. 5B shows that P.L. had no difficulty remembering the shapes, performance being equal to controls at all delays.

DISCUSSION

We have shown that P.L. can store, rehearse and recall colour names normally, provided they are presented verbally (Experiment 1). On the other hand, in subsequent tasks, where the stimuli were patches of colour, P.L. demonstrated severe impairments. Analyses of errors and interference revealed that P.L., like normal controls, employed a verbal coding strategy in these tasks, that is, he covertly named the presented colours and retained the verbal labels in short-term memory. Since P.L. frequently names colours incorrectly, he often commits wrong and misleading labels to verbal short-term memory resulting in very poor performance in these tasks.

Why did P.L. not turn to a visual strategy in the tasks where patches of colour were used? This question is particularly pertinent since Experiment 3 demonstrated that for normals a useful visual trace is available for at least 8 s in the absence of visual interference. In Experiment 3, however, we also showed that P.L.'s visual short-term memory for colours is impaired to such an extent that performance drops to chance level within a few seconds. Therefore, P.L. is unable to compensate for his inaccurate verbal labelling by using visual storage.

P.L. has a naming deficit limited to colours and we have found a visual short-term memory impairment limited to colour information. It is, of course, possible that these impairments are functionally independent but for them to be connected is both parsimonious and offers an explanation of the phenomenon of preserved pointing in the face of severely impaired naming. No alternative account of the colour anomia seems capable of explaining preserved pointing to named colours; a general disruption of the lexical system should affect pointing as well as naming; there is no evidence of a generalized word-finding problem, affecting both objects and colours, which would always make pointing easier than naming; a perceptual explanation, invoking a failure to discriminate between the colours, should affect pointing and naming equally. Therefore we believe that this defect of visual short-term memory for colours could be the functional cause of his colour anomia. The abnormally weak short-term memory trace prevents sufficient information from reaching the colour lexicon to activate the appropriate entry and therefore naming is largely determined by noise in the system. If verbal and visual input converge on the same lexical system, verbal input should be capable of activating or priming an entry in the lexicon and therefore, pointing to a named colour is possible. The verbal name activates (primes) the appropriate entry in the lexicon and little additional visual information is required to trigger this already primed entry. This model of pointing and naming of colours is illustrated in fig. 7.

Visual input is retained in a colour specific short-term store while information is transferred to the colour lexicon. When sufficient information has accumulated in the lexicon the first entry above threshold will trigger, making the appropriate response available. In P.L.'s case, the visual trace is weak and short lasting and, consequentially, most of the information reaching the colour lexicon is noise resulting in inaccurate naming responses. However, when asked to point to a named colour, the verbal input primes the appropriate entry in the colour lexicon and even the very limited amount of visual information which can be extracted from P.L.'s defective short-term memory is sufficient to elicit the correct response.

This model of P.L.'s colour anomia produces two clear and testable predictions. First, that the most frequent name given to a colour should be the correct one, even the weakened visual signal makes some contribution. Table 3 shows that this is indeed the case. Secondly, that within a relatively short interval after being asked to point to a colour, P.L. should be able to name this colour. A final experiment was designed to test this prediction.

In this experiment we alternated between pointing to a named colour and naming a coloured patch. Two coloured patches were presented and P.L. was asked to point to one of them. The two patches were removed and within 2 s a third patch was presented and P.L. was asked to name this colour. This was repeated with different colours for 60 trials. On one-third of the trials (priming trials), the colour to be named was of a different hue but of the same name as the colour just pointed to, while on the remaining trials pointing and naming involved colours of different names. It is emphasized that in priming trials, the colour to be named and the colour

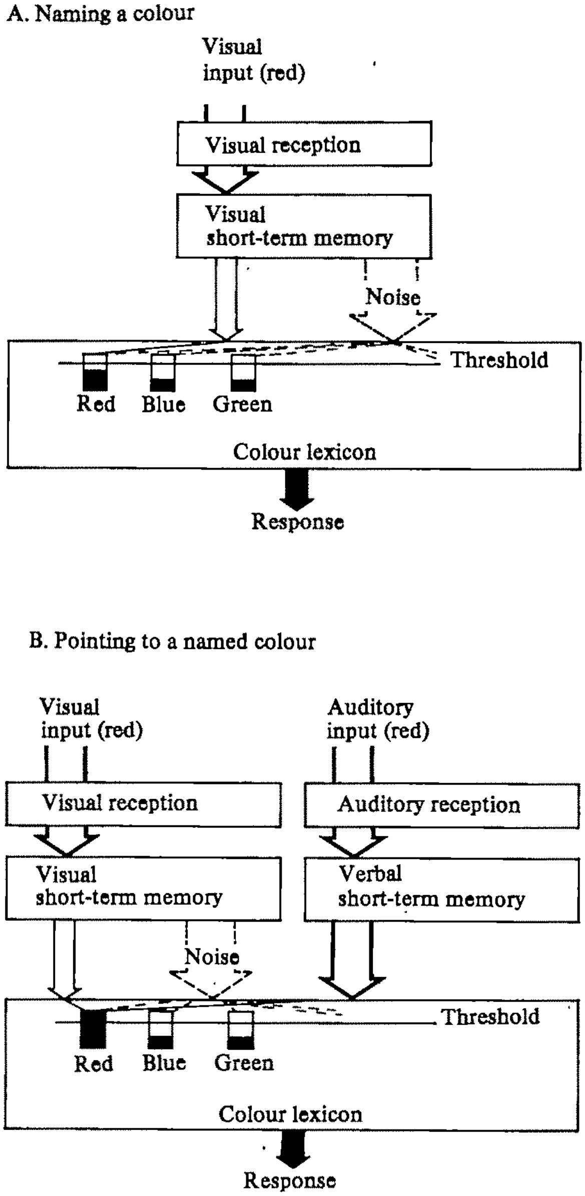


FIG. 7. Diagrammatic representation of the functional disturbance responsible for A, P.L.'s inability to name colours while B, allowing his preserved ability to point to a named colour.

pointed to, although having the same name, were never physically identical. To assess the persistence of possible priming, the task was repeated with an additional irrevelant pointing trial intervening between pointing and naming.

It is seen in Table 5 that P.L. performed according to the prediction of the model. On 90 per cent of the trials he was able correctly to name a colour of a different hue but of the same name as the colour to which he had just pointed (the primed condition). In the random trials, on the other hand, where naming and pointing involved colours of different names he correctly named only 60 per cent of the colours. There was no perseveration of naming the colour to which he had just pointed. The difference between these two conditions was significant, $\chi_1^2 = 5.71$, $P < 0.02$. It is also seen that the effect of priming is very short lived, with just one intervening irrelevant pointing trial (delayed condition) his performance in the primed condition was no better than in the unprimed condition ($\chi_1^2 = 0.02$, n.s.).

TABLE 5. THE EFFECTS OF PRIMING BY POINTING ON P.L.'S NAMING OF COLOURS

	Primed condition	*Random condition*
Immediate naming	90%	60%
Delayed naming	55%	57%

It could be asked why P.L. did not prime himself in colour-naming tasks when he knew that a limited set of 10 colours was used, that is, by going through the colour names one by one. This would not benefit performance because he would need to make comparisons between lexical entries that were primed correctly and those primed incorrectly. Thus he would still have to select his response on the basis of his poor visual input. If the prime is given to P.L. (as in point to the 'red') only one entry, the correct one, in the lexicon is activated. The difference between correct and incorrect entries is then considerable and response selection consequently easy.

CONCLUSIONS

We do not believe that P.L.'s residual colour naming and almost perfect naming with priming is carried out by an inferior right hemisphere language system because a full range of colour names is produced. Therefore colour information must be transmitted to the left hemisphere by one of two routes. From the CT scan (fig. 1) it might seem unlikely that transfer occurs *via* the splenium as normally. However, the alternative explanation of transfer *via* the intact anterior commisures would seem improbable given their usual functions. It would therefore appear that, especially given the limited extent of his alexic disturbance, there are spared splenial fibres. In cases of alexia without agraphia where colour naming is preserved there is indeed some evidence of intact dorsal fibres in the splenium (Cumming *et al.*, 1970; Greenblatt, 1973). Furthermore, an explanation of the colour deficits in terms of a

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INCREASE IN AXONAL TRANSPORT IN DEMYELINATING OPTIC NERVE FIBRES IN THE MOUSE INFECTED WITH SEMLIKI FOREST VIRUS

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SUMMARY

Since the integrity of myelin and axon is closely linked with the transport of substances along the axon, changes in the fast and slow axonal transport in the demyelinating optic nerves of mice infected with Semliki Forest virus were studied. Radioactive analysis of the superior colliculi and the optic nerves was thus made following different survival times after an intravitreal injection of tritiated proline by autoradiographic and liquid scintillation counting techniques. The amounts of both the fast and slow axonal transport of proteins were significantly higher in the optic nerves of mice infected with the virus than those found in the optic nerves of control mice. These results suggest that demyelinating fibres send a signal to the perikarya which then responds by synthesizing more proteins.

INTRODUCTION

It has become increasingly evident that the relationship between a neuron and its myelin sheath, involving the transfer of substances from axon to myelin and myelin to axon, is closely linked with the transport of substances along the axon (Gainer, 1978; Droz, 1979; Kriegler *et al.*, 1981). Changes in axonal transport have been described in dystrophic animals with abnormal myelination (Bradley and Jaros, 1973; Kuffer *et al.*, 1977), and there is also evidence that demyelination induced by diphtheria toxin (Kidman *et al.*, 1978) or chronic demyelination related to experimental allergic encephalomyelitis (Rao *et al.*, 1981) affects axonal transport. However, the observations made on the influence of myelination on axonal transport differ widely, ranging from blockade (Kidman *et al.*, 1978), significant reduction (McLane and McClure, 1977), to an increase (Bradley and Jaros, 1973; Komiya and Austin, 1974; Kuffer *et al.*, 1977; Rao *et al.*, 1981) of fast axonal transport. A differential effect on fast and slow transport has also been reported (Bradley and Jaros, 1973; Kidman *et al.*, 1979; Rao *et al.*, 1981). It is therefore difficult to form any general conclusions as to the nature of changes in axonal transport in nerve fibres in which the integrity of myelin is disrupted. It is possible that the major differences in the results are simply due to the diversity of the animal models used in these previous studies.

In a previous paper (Tremain and Ikeda, 1983), we have emphasized the suitability of mice infected with Semliki Forest virus (SFV) as an animal model for studying the underlying mechanisms of demyelinating disease in man for the following three reasons. (1) SFV has similar viral features to measles virus (Andrewes *et al.*, 1978), specific immunity to which has been found in patients with multiple sclerosis (Adams and Imagawa, 1962; Brody *et al.*, 1972; Haire, 1977). (2) SFV infection in mice produces patchy demyelination in many different locations within the CNS as is observed in patients with multiple sclerosis (Chew-Lim *et al.*, 1977). (3) There is a close similarity between the physiological deficits in the visual system of mice infected with SFV and those in patients with demyelinating diseases (Tremain and Ikeda, 1983).

The present study reports the results of an analysis made on fast and slow axonal transport in the demyelinating optic nerve of mice infected with SFV. A preliminary report has already appeared (Pessoa and Ikeda, 1982). We have previously established the extent and degree of demyelination produced by SFV in a controlled anatomical study with the microdensitometry technique (Fleming *et al.*, 1982).

METHODS

Infection Procedure and Control Mice

A total of 180 albino mice of both sexes weighing 25–45 g were used (St Thomas' Hospital Medical School strain, originally bred from Swiss A2 G mice). Of these, 90 received intraperitoneal injections of avirulent SFV (0.1 ml in 10^{-4} dilution of bovine albumin phosphate saline (BAPS)) and 90 control mice received 0.1 ml of BAPS only, at 4 and 6 weeks of age. The reason for giving two injections at these ages was that this method has been used by previous investigators (Chew-Lim *et al.*, 1977) and was found to produce patchy demyelination in the cerebellum and the brainstem, although only one inoculation can cause similar results (Suckling *et al.*, 1978). The viability of the virus was first checked by inoculating 0.02 ml SFV in 3 to 4 day-old mice intracerebrally. Only the virus samples which killed newborn mice within two to three days were used.

Axonal Transport Studies

Intraocular injection of radioactive proline. Seven days after the second inoculation with SFV or with the control solution, each mouse received an intravitreal injection of 1 to 2 μl of L-(3,4[n]-^{3}H) proline under short-acting general anaesthesia induced by Sagatal (45–50 mg/kg i.p.). The concentration of (^{3}H) proline (Amersham) was 1 mCi/ml, and its specific activity was 40 to 60 Ci/mmol. Because of the small size of the mouse eye, the intraocular injection was performed under a stereo-operating microscope using a glass pipette, with a sharp tip of 60 μm attached to a hydraulic system. The pipette was inserted at about 0.7 mm behind the limbus margin of the eye ball at an angle of 40 to 50 deg with reference to the equator of the eye ball which is laid as horizontal as possible so that the line of the equator is perpendicular to the optical axis of the eye. To prevent a rapid increase in the intraocular pressure, the injection was made very slowly over a period of approximately 2 min.

Survival periods. The mice which received a (^{3}H) proline injection recovered from the anaesthetic within 1 h. Care was taken to maintain the body temperature of the mice throughout this period by laying them on a heating pad set at 37.5° C. The animals were allowed to survive for different periods ranging from 1 h to 20 days.

Four to 6 deeply anaesthetized mice were killed by decapitation at 1, 2, 3, 5, 8, 12, 18, 24 or 48 h after the intravitreal injection of proline, for the fast axonal transport studies. Similarly, samples of 4 to 6 mice were killed at 2, 3, 4, 5, 6, 8, 10, 12, 14 or 20 days after the injection for the slow axonal transport studies. The brains and optic nerves were removed rapidly from the mice and stored in 10 per cent buffered formalin for two to three weeks. It has been shown that after formaldehyde fixation, little, if any unincorporated label persists in the tissues (Hendrickson and Cowan, 1971).

Radioactive analysis of the superior colliculus by liquid scintillation counting. From each mouse brain, the entire superior colliculus in the hemisphere contralateral to the eye into which the radioactive proline had been injected and that ipsilateral to the injected eye were removed and put into separate containers. Since approximately 97 per cent of the optic nerve fibres cross to terminate in the contralateral superior colliculus (Dräger and Olsen, 1980), the contralateral superior colliculus was considered as the experimental target and the ipsilateral superior colliculus as the control structure for the axonal transport investigation.

Each superior colliculus sample was air dried, weighed to the nearest 0.1 mg, and solubilized overnight at 50° C in S-350 (Packard). Radioactivity was measured using DM-30 scintillation fluid (Packard) in an LKB liquid scintillation counter with a counting efficiency for tritium of the order of 40 per cent. After determining the corrections for quenching, the tissue activity was expressed in terms of disintegrations per minute per μCi of isotope injected per mg of dry tissue (dpm/μCi/mg). The final axonal transport values were obtained by the difference in radioactivity found between the contralateral and ipsilateral superior colliculus.

Autoradiographic and Microdensitometric Studies of Axonal Transport in the Optic Nerve and the Superior Colliculus

To study slow axonal transport in the optic nerves by autoradiography, the optic nerves were removed from the control and infected mice under deep anaesthesia four days after proline injection into the vitreous chamber of the eye. Survival periods of 16 h and 10 days respectively were, on the other hand, used for visualizing and measuring fast and slow transport at the superior colliculus. The optic nerves were fixed in buffered paraformaldehyde and the brains in 10 per cent formol saline for two weeks. The optic nerves of the injected eye from a control and an infected mouse were paired and embedded in araldite and transverse sections were cut at 1 μm thickness. Frozen sections of the brains at 20 μm thickness were cut in the coronal plane at the level of the superior colliculus. These sections were mounted on slides and processed by the standard autoradiographic technique using Ilford K-2 emulsion and developed with Kodak D-19 for 4 min at room temperature. Exposure time ranged from three to four weeks.

The density of grains was measured using a sampling spot of 190 μm in diameter of a scanning microdensitometer (M86 Vickers Instrument) in both contralateral and ipsilateral superior colliculi of 6 control-infected pairs of unstained sections cut at the frontal plane A 0.8. Of the 6 pairs, 3 were taken from mice killed at 16 to 18 h after the intraocular injection of (^{3}H) proline and 3 from those killed at 7 to 10 days after the injection. At the frontal plane, A 0.8, the superior colliculus of the mouse stretched approximately 2300 μm mediolaterally and 400 μm dorsoventrally. Usually 12 points along the dorsal surface curvature were measured.

RESULTS

Study of Fast Axonal Transport by Liquid Scintillation Counting

Fig. 1A shows the amount of radioactivity found in the contralateral and ipsilateral superior colliculus at different intervals after injection of (^{3}H) proline

(1–2 μl) in one eye of control mice. This first peak corresponds to the usual fast component of protein transport shown for the mouse (Grafstein *et al.*, 1972). The control mice received i.p. injection of 0.1 ml bovine albumin phosphate saline at 4 and 6 weeks of age, and the intravitreal proline injection when they were 7 weeks old.

The radioactivity found in the ipsilateral colliculus was extremely low but this is what would be expected because about 97 per cent of the optic nerve fibres are crossed in mice (Dräger and Olsen, 1980). The fast amino acid transport by the crossed fibres appeared to reach a maximum at 8 to 12 h after the substance was injected into the vitreous chamber. The peak activity was about 2300 dpm/μCi/mg.

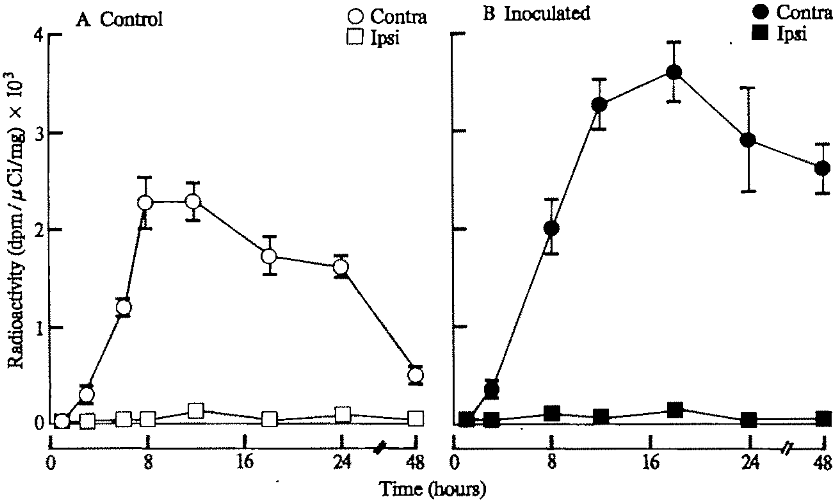

FIG. 1. Fast axonal transport in the optic nerve determined by radioactivity counted in contralateral (contra) and ipsilateral (ipsi) superior colliculus samples at different intervals after injection of (^{3}H) proline into one eye of control (A) and SFV infected (B) mice. Each point in the graphs represents the mean and standard error of 4–6 samples. Note that the activity is very low in the ipsilateral superior colliculus due to the fact that 97 per cent of the retinocollicular fibres are crossed in the mouse.

Fig. 1B shows the amount of radioactivity found in the superior colliculus of the SFV infected mice. As in the control brains, the ipsilateral superior colliculus showed negligible radioactivity throughout, whereas the transport to the contralateral superior colliculus was significant. In addition, the amount of radioactivity found in the contralateral superior colliculus of the infected mice was much higher (3600 dpm/μCi/mg) than that found in the contralateral superior colliculus in the control mice. This comparison is seen more clearly in fig. 2 in which the differences in the fast axonal transport between the contralateral and ipsilateral superior colliculus were plotted for the infected mice and the control mice. The difference in radioactivity between the control and the infected mice at each survival time (fig. 2) was significant at 18, 24 and 48 h after the injection (paired t test).

Whereas the peak activity occurred in the control side at about 8 to 12 h after the injection, that in the infected side occurred at 16 to 18 h. The peak activity found in the infected colliculus is, furthermore, over 3600 dpm/μCi/mg compared with 2300 dpm/μCi/mg in the control. In other words, approximately 63 per cent more protein has been transported by the infected nerve than in the control nerve. However, the rate of transport in terms of initial slope of the curve does not differ greatly between the control and infected nerve transport. The initial appearance of labelled protein in the superior colliculus in both control and infected mice occurred at 2 to 3 h after the injection in the eye. The distance between the eye and the superior colliculus of our mice is approximately 16 mm. The calculated maximum and average rates of the fast axonal transport using the methods adopted by Grafstein and Laureno (1973) are, therefore, 192 mm/day and 69.8 mm/day in the control mice, and 192 mm/day and 45.1 mm/day in the infected mice, respectively.

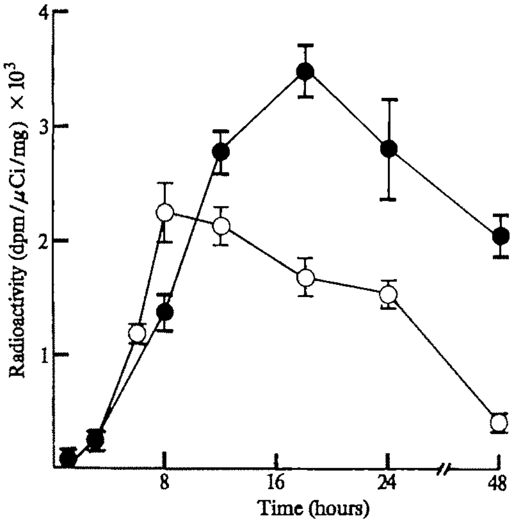

FIG. 2. Comparison of fast axonal transport in optic nerves of control (open circles) and SFV infected (closed circles) mice. Each curve represents the difference of the radioactivity found in the contralateral and in the ipsilateral superior colliculus, that is, the difference of the two curves in fig. 1A (control) and 1B (inoculated).

Study of Slow Axonal Transport by Liquid Scintillation Counting

Fig. 3A shows the amount of radioactivity found in the contralateral and ipsilateral superior colliculus of control mice at different intervals after the decline of the fast axonal transport. Again no significant radioactivity can be seen in the ipsilateral superior colliculus. The large peak (around 4800 dpm/μCi/mg) appearing at 8 to 12 days after the intravitreal injection of the substance in the contralateral superior colliculus represents the conventional slow transport with a rate of 1 to 2 mm/day. Other possible peaks can be seen at 3 to 4 days which might represent a component of intermediate rate (Grafstein and Laureno, 1973) and at 14 days after the injection there is still considerable radioactivity. Although it is not shown in the figure, the level was still well above the control level at about 20 days after injection.

Fig. 3B shows the strikingly high level of activity in the contralateral superior colliculus of the infected mice with the peak activity reaching 8000 dpm/μCi/mg at 10 to 12 days after the injection. Again, no or little activity was found in the superior colliculus ipsilateral to the injected eye. The intermediate peak seen in the control curve does not appear in the infected mice curve. This is probably due to the slow decline of the fast component and the enormous quantity of slowly migrating component masking the intermediate transport peak. As Grafstein and Laureno (1973) pointed out, the putative intermediate component of axonal transport is not a reproducible phenomenon in small animals such as the mouse.

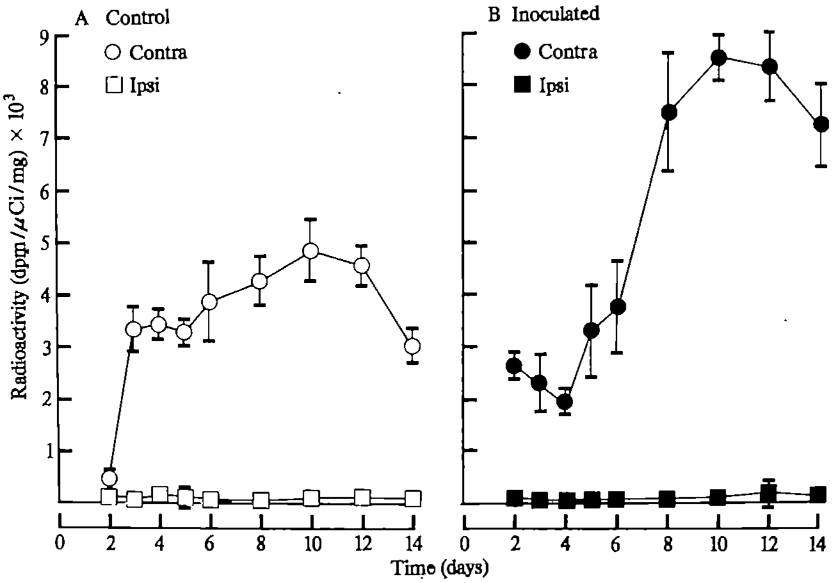

FIG. 3. Slow axonal transport in the optic nerve determined by radioactivity counts in the contralateral (contra) and ipsilateral (ipsi) superior colliculus samples collected at different intervals after injection of (^{3}H) proline into one eye of control (A) and SFV infected (B) mice. Each point in the graph represents the mean and standard error of 4–6 samples.

In fig. 4 the differences in slow axonal transport found between the contralateral and ipsilateral superior colliculus were plotted for the infected mice and the control mice. The amount of radioactivity in the infected brain is almost doubled compared with that in the control brain, although the peak is reached at about the same time. The curve for the infected nerve shows an initial fall between 2 and 4 days after the intravitreal injection of proline. The fall represents a process of decay of fast axonal transport. Both fast and slow axonal transport are significantly increased in the optic nerve fibres in which demyelination is produced by virus infection.

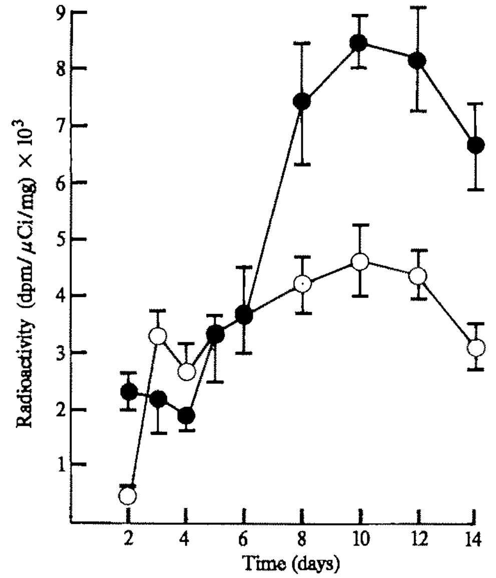

FIG. 4. Comparison of slow axonal transport in optic nerves of control (open circles) and SFV infected (closed circles) mice. Each curve represents the difference of the radioactivity found in the contralateral and in the ipsilateral superior colliculus, that is, the difference of the two curves in fig. 3A (control) and 3B (inoculated).

Autoradiographic Confirmation of the Increase in Fast and Slow Axonal Transport in the Optic Nerve of Mice Infected with SFV

Liquid scintillation counting revealed that both fast and slow axonal transport along the optic nerve were significantly increased at the contralateral superior colliculus in the SFV infected mice. Confirmation of the increase by autoradiography was therefore sought.

Fig. 5A shows a pair of coronal sections of the mesencephalon cut at the level of the superior colliculus. One is taken from a control mouse and the other from an infected mouse 16 h after the intraocular injection of (^{3}H) proline, given 7 days after the second viral inoculation. Fine grains of radioactive labelling can be seen in both sections but the labelling is much more intense in the SFV infected than in the control superior colliculus, confirming the result of liquid scintillation counting that fast axonal transport is increased.

In fig. 5B an autoradiographic picture of the superior colliculus sections taken from a control mouse and from a SFV infected mouse brain 10 days after the proline injection in the contralateral eye are compared. Again, the labelling is considerably denser in the contralateral superior colliculus of the SFV infected mouse than in the control mouse, confirming the liquid scintillation counting result that slow axonal transport is also enhanced in the demyelinating optic nerve of the infected mouse. The slow transport labelling (5B) is much greater than that for fast transport (5A) and again this confirms the results with liquid scintillation counting.

It is difficult to compare fast axonal transport at the level of the optic nerve in small animals such as the mouse, with a prechiasmal optic nerve length of 6 mm, when the transport occurs at 3 to 8 mm/h (i.e. 70–192 mm/day). But it is possible to

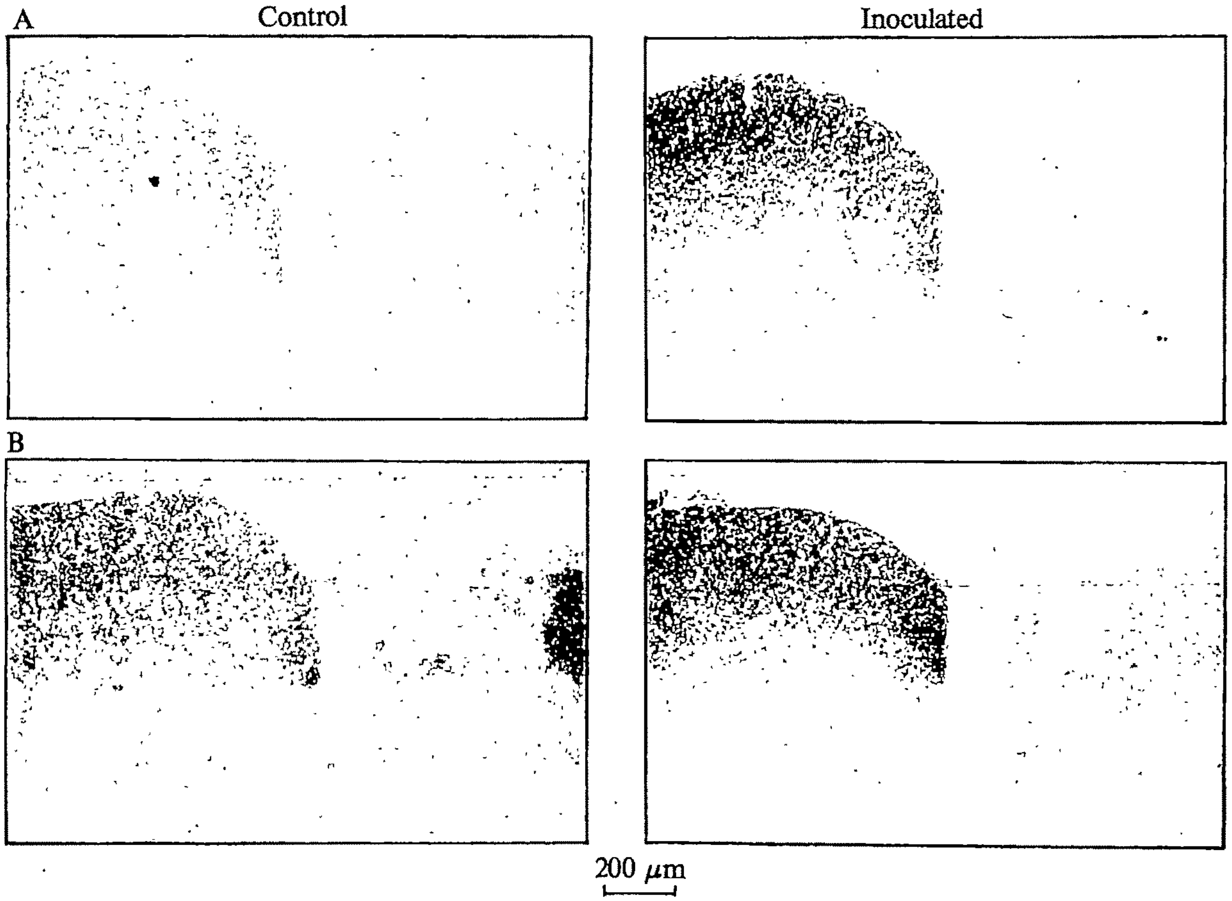

Fig. 5. Bright-field autoradiographs of coronal sections cut through the superior colliculus of the brain, prepared 16 h (A) and 10 days (B) after injection of (^{3}H) proline into one eye. Dense radioactivity is seen at the contralateral superior colliculus and the activity is higher in the SFV infected mouse brain than in the control brain.

capture slow transport at 3 to 4 days after the intravitreal injection of (^{3}H) proline when the migrating labelled substance is fairly evenly distributed throughout the nerve. Fig. 6 shows an example of light field autoradiographs of paired unstained optic nerve transverse sections, the left from a control mouse and the right from an inoculated mouse. In the low magnification photographs it is not possible to see the radioactively labelled grains. The two pairs of autoradiographs of higher magnification show the central portion (A) and the peripheral portion (B) of the optic nerve as indicated in the upper photographs at a low magnification. The density of grains is higher in the optic nerve of the infected mouse than in the control nerve for both the central and the peripheral areas.

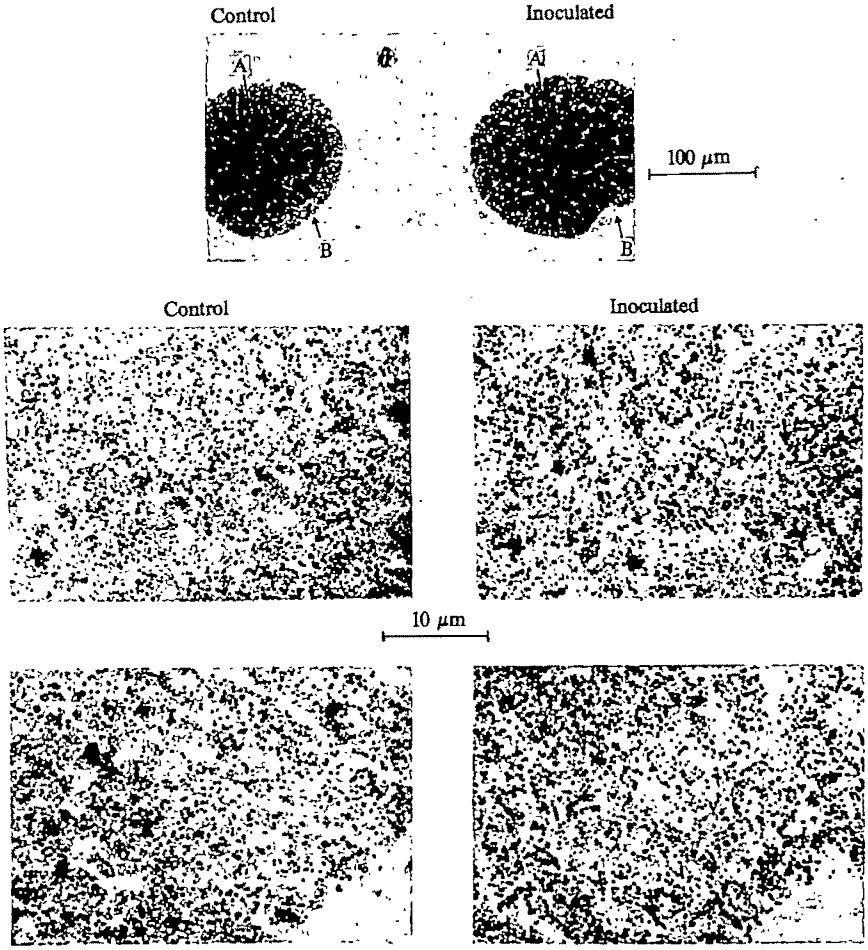

Fig. 6. Bright-field autoradiographs of optic nerve sections from a control and a SFV infected mouse, prepared 4 days after intraocular injection of (^{3}H) proline. The sections were not stained. The top picture shows the two nerves processed simultaneously. Arrows indicate the location within the nerve from which the enlarged pictures were taken. Note that the grain density in the nerve of the SFV infected mouse is higher than that in the control nerve section.

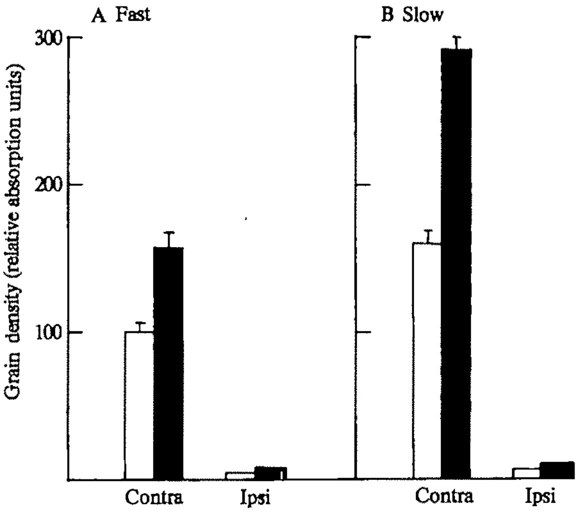

FIG. 7. Microdensitometry measurements of the labelled grains in unstained coronal sections of control (open square) and infected (closed square) brains at the superior colliculus level (AP 0.8) and processed as a pair for autoradiography. Each bar of the histogram represents the mean and standard error of the three sections analysed in the Table. Contra = contralateral and ipsi = ipsilateral superior colliculus.

In order to quantify the difference between the grain density of the radio-labelled protein in the control and in the infected superior colliculus, microdensitometry was carried out in 3 pairs of superior collicular sections at AP 0.8. The results are summarized in the Table in which the grain density for each specimen is shown. The intensity of labelling was evaluated, estimating the relative absorption of light by unstained histological sections. The greater the grain density, the greater is the absorption of light. Although relative absorption values varied from sections of one mouse to those of another, in each of the 3 control and inoculated section pairs, the difference was statistically significant.

Fig. 7 shows combined results of the 3 control and infected pairs of superior collicular sections analysed in the Table. Since 12 sampling areas were used for the measurement in each superior colliculus, each bar of the histogram in fig. 7 is the mean and standard error of 36 measurements. The difference between the grain density found in the control and infected contralateral superior colliculus was statistically significant ($P < 0.001$) for both fast and slow axonal transport.

TABLE. MICRODENSITOMETRY MEASUREMENTS IN THE SUPERIOR COLLICULUS

	Control			*Inoculated*		
Sample	*Contralateral*	*Ipsilateral*	*Difference*	*Contralateral*	*Ipsilateral*	*Difference*
Fast transport						
1**	99.3 ± 11.5	3.8 ± 1.0	95.5	176.4 ± 17.5	8.5 ± 1.5	167.9
2*	129.0 ± 14.3	6.8 ± 1.1	122.2	179.1 ± 18.3	8.0 ± 1.1	171.1
3*	84.8 ± 8.0	1.7 ± 0.3	83.1	116.8 ± 7.9	8.6 ± 1.1	108.2
Slow transport						
1**	146.2 ± 11.4	9.1 ± 0.7	137.1	310.1 ± 27.7	9.3 ± 1.2	300.8
2**	179.3 ± 12.8	7.1 ± 0.9	172.2	275.5 ± 22.9	10.2 ± 0.8	265.3
3**	156.0 ± 12.1	10.4 ± 1.3	145.6	288.8 ± 18.7	12.4 ± 1.4	276.4

** = $P < 0.001$. * = $P < 0.02$.

Although the grain density is significantly low in the ipsilateral superior colliculus, again the grain density was higher in the infected superior colliculus than in the controls ($P < 0.025$).

DISCUSSION

Axonal Transport and Demyelination

Our enquiry into what happens to axonal transport in the optic nerve of SFV infected mice was 'open-ended', since no previous studies have been made on axonal transport in virus-induced demyelination. However, the answer which we obtained was surprisingly clear-cut. Both fast and slow axonal transport increased in the demyelinating optic nerve of the infected mouse.

It appears that our finding that fast axonal transport is increased in demyelinating optic nerve fibres of SFV infected mice is consistent with the increase in fast axonal transport in dystrophic mice with abnormal myelination (Bradley and Jaros, 1973; Komiya and Austin 1974; Kuffer *et al.*, 1977) and of experimental allergic optic neuritis in guinea pig (Rao *et al.*, 1981). Although McLane and McClure (1977) reported the contrary result, namely, a decrease in fast axonal transport in the sciatic nerve of dystrophic mice, these observations were mainly made *in vitro*.

There are only two studies on slow axonal transport in animal models of demyelination, both of which showed a decrease rather than an increase in transport (Bradley and Jaros, 1973; Rao *et al.*, 1981) and this is contradictory to our finding. It is difficult even to speculate why fast and slow axonal transport should be different in virus-induced patchy demyelination. Perhaps there is a difference in the axonal transport between the virus-induced demyelination and allergic encephalomyelitis or genetically induced demyelination.

Axonal Transport and Conduction Velocity in Demyelinating Fibres

There appear to be no studies on the relationship between conduction velocity of action potentials and axonal transport of normal nerve fibres in the CNS. However, in the demyelinating nerve fibres of SFV infected animals, an increase in axonal transport and a decrease in conduction velocity seem to be asociated. Tremain and Ikeda (1983) clearly demonstrated that conduction along the demyelinating optic nerve of SFV infected mice is slowed. A decrease in conduction velocity in various nerves in experimental allergic encephalomyelitis has been reported by many investigators (Hall, 1967; Davis, 1972; Kraft, 1975; Hayreh *et al.*, 1981). Rao *et al.* (1981) showed an increase in fast axonal transport in his animal model of experimental allergic encephalomyelitis.

Similarly, in dystrophic mice with abnormal myelination an increase in axonal transport (Komiya and Austin, 1974, 1975) and a slowing of conduction velocity in the spinal cord (Biscoe *et al.*, 1977; Martin *et al.*, 1978) have been demonstrated.

The mechanism of slowing or failure of conduction in demyelinated nerve fibres is well established (McDonald and Sears, 1970). However, why is axonal transport increased?

Possible Mechanisms Underlying the Increase in Axonal Transport in Demyelinating Optic Nerve Fibres in SFV Infected Mice

It is known that trophic interactions of neurons and glia are bidirectional and substances transported retrogradely may carry feed-back 'messages' from the axons to the cell body (*see* Kriegler *et al.*, 1981). The optic nerves of SFV infected mice were undergoing demyelination at the time of our axonal transport study and there were some infiltrating mononuclear cells, hypertrophic astrocytes and myelin debris in the extracellular space of the optic nerve of infected mice (Fleming *et al.*, 1982; Illavia *et al.*, 1982). Such pathological changes associated with demyelination possibly trigger feed-back 'messages' to the retinal ganglion cell bodies and increase protein synthesis at the cell body to enhance axonal transport. According to Murray and Grafstein (1969), Heacock and Agranoff (1976) and McQuarrie and Grafstein (1982), an increase in axonal transport is associated with an increase in protein synthesis at the cell body. It will be of interest to establish whether an increase in protein synthesis occurs in the ganglion cells in SFV infected mice.

On the other hand, an increase in axonal transport is often associated with the process of regeneration of some fibres after nerve damage (Wolburg, 1981; McQuarrie and Grafstein, 1982). Protein and glycoprotein in sprouting optic nerve fibres have been shown to be incorporated into the axolemma at higher levels than in parent axons, thus leading to enhanced axonal transport (*see* Grafstein and Forman, 1980).

We have now electron microscopic evidence that there is an increased number of small (less than 0.2 μm in diameter) unmyelinated axons occurring in clusters in the optic nerves of mice infected with SFV (S. Fleming, E. M. Tansey, V. F. Pessoa, D. N. Landon and H. Ikeda, unpublished results).

There is another factor which may have influenced our results. Since the accumulation of the transported proteins at the terminal results from a balance between its arrival and its turnover (Ochs, 1982), the increase in radioactivity found at the superior colliculus of SFV infected mice might have represented a reduction in turnover of the labelled protein, rather than representing a true increase in axonal transport. Only studies of retrograde axonal transport, biochemical analyses of metabolic breakdown of proteins and autoradiographic analyses of transneuronal transfer of substances at the optic nerve terminals in the animal model of demyelination can answer the question.

Is the Increase in Axonal Transport a Cause or a Result of Demyelination?

Our discussion so far has been based on the assumption that the increase in axonal transport is a result of demyelination, since our axonal transport studies were undertaken at the expected peak of demyelination (Chew-Lim *et al.*, 1977; H. E.

Webb, personal communication). However, we must consider the possibility that changes in axonal transport may precede demyelination as it is also possible that the changes in axonal transport may be related to the cause of demyelination due to direct virus infection. Further work in studying axonal transport at different stages of the infection is required to clarify this point. The precise time course of changes in axonal transport and physiological and anatomical changes in SFV infected mice may help us to understand the underlying mechanism of virus-induced demyelination.

ACKNOWLEDGEMENTS

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blood flow (rCBF) is reduced in the brain during attacks was later supported by direct measurements of rCBF (Skinhøj, 1973; Sakai and Meyer, 1978). How this blood flow reduction develops was recently studied by us in two series of patients with classical migraine who underwent carotid angiography as part of the clinical evaluation. The angiography in some cases triggered attacks when rCBF was measured by Xenon-133 injections in the internal carotid artery. The hypoperfusion of classical migraine was shown to develop in a wave-like fashion, starting in the posterior part of the brain (Olesen *et al.*, 1981*a*). The hypoperfusion progressed anteriorly at a rate close to 2 mm/min and did not cross borders of major macro- or microstructural changes, that is, at the primary sulci. This pattern appeared to be causally related to the syndrome of classical migraine, and it may be a manifestation of the spreading depression of Leão (Lauritzen *et al.*, 1982, 1983*a*). In attacks of common migraine, induced by drinking red wine, rCBF was studied with the atraumatic technique employed in the present study. Intracranial blood flow remained normal, indicating a different pathogenesis for the two syndromes (Olesen *et al.*, 1981*b*).

The aim of the present study was to investigate rCBF during spontaneously occurring migraine attacks as they present themselves in an acute headache clinic. The development of a safe, atraumatic method for cerebral blood flow studies has made this possible. Single photon emission computerized tomography after inhalation of Xenon-133 has been shown to be a valid method for the determination of alterations of rCBF in stroke and transient ischaemic attacks (Lassen *et al.*, 1981; Vorstrup *et al.*, 1983). The three-dimensional approach circumvents tissue layer superposition and allows distinction of blood flow in cortical and subcortical regions. We studied 23 patients with classical and common migraine during their spontaneous attacks to elucidate the localization and duration of flow changes, and the possible difference between the two syndromes.

MATERIAL AND METHODS

The subjects consisted of 23 patients attending the Copenhagen Acute Headache Clinic for treatment of a migraine attack. Medical history and examination were obtained before investigation, using a standard chart (Olesen *et al.*, 1979). At re-examination at least one week after the first blood flow measurement, a full history was taken and a neurological examination was performed.

Patients were selected for the study when they had symptoms of (1) common migraine, that is, recurrent idiopathic headache with nausea and one or more of the following symptoms, pulsatile pain, unilateral headache, or phono- or photophobia, or (2) classical migraine, that is, recurrent attacks of headache preceded or accompanied by symptoms of focal neurological dysfunction such as aphasia, scintillations, hemianopia, loss of monocular vision, paraesthesiae, hypaesthesia, hypalgesia and paresis. It was also required that they suffered from migraine according to the definition of the Ad Hoc Committee of the National Institutes of Health (Ad Hoc Committee on Classification of Headache, 1962). Patients were excluded if (1) they had symptoms or signs of other somatic or psychiatric illness, (2) they were less than 18 or more than 65 years old, (3) they suffered from more than four attacks monthly, (4) they had interval headache more than once a week, (5) they had taken preparations with known effects on the cerebral circulation, (6) the present attacks had lasted for more than 24 h, or

(7) they were pregnant. All patients who met our inclusion criteria were investigated in the present study. The clinical data of the patients are given in Tables 1, 2, and 5.

rCBF was measured 1 to 5 times at 20 to 45 min intervals before treatment, then after 0.25 mg ergotamine and 10 mg of metoclopramide i.m. when symptom-free and after being free from migraine for at least one week. During the study patients were supine, with eyes closed, and the room dark and quiet to achieve a state of minimal external stimulation.

Before investigation, informed consent was obtained after full explanation of the procedure, including the radiation hazards. Xenon-133 is administered by inhalation and the radiation dose to the lungs, the target organ, is only 0.36 rad for a 1 min Xenon-133 inhalation (Atkins *et al.*, 1980), that is, less than when taking a conventional chest x-ray.

Cerebral blood flow was measured by the Xenon-133 inhalation method, using rapidly rotating single photon emission tomography. The instrument has 64 sodium iodide crystals, each measuring 12 cm in length, 1.3 cm in width and 2.0 cm in depth. They are arranged in four banks that look at the brain from four sides. The geometric arrangement yields with this collimation a sensitivity of 18 000 counts.s^{-1}/slice for a 20 cm wide and circular, waterfilled phantom containing 1 μCi/ml Xenon-133, using a 20 per cent energy window. The lead collimators focus on three slices of brain tissue approximately 2 cm thick and spaced with a distance of 4 cm between the midslice planes (Stokely *et al.*, 1980). By appropriate placing of the patient in the 20 cm wide aperture of the tomograph, the midplanes of the 3 slices are regularly positioned 1, 5 and 9 cm above the orbitomeatal plane. Each CBF study lasts for 4 min during which a series of four consecutive 1 min periods are recorded. Xenon-133 is rebreathed throughout the initial 1.5 min in a closed system with a concentration of 10 mCi/l. The isotope concentration of the lung is followed by a stationary scintillation detector placed over the right upper chest. With this isotope concentration, the counting rate is close to 400 000 in the second minute when it is at its maximum. At this counting rate, the resolution in the plane is 1.7 cm, expressed as full width of a point source measured at its half maximum counting rate.

The air-curve from the right upper lung and the four 1-min recordings are used for the calculations of CBF by a deconvolution procedure (Kanno and Lassen, 1979; Celsis *et al.*, 1981). It is in essence an *in vivo* modification of the Kety autoradiographic method (Kety, 1951). The calculations assume a fixed value of lambda of 0.85 ml/g in all areas. This lambda value corresponds for patients with a normal haemoglobin concentration to lambda for grey matter, that is, the high flow areas of the brain used to scale the flow in absolute units of ml/100 g/min (Celsis *et al.*, 1981). The end-expiratory CO_2 concentration is measured in the third and fourth minute of the washout period by an infrared analyser. Blood pressure is measured immediately after the investigation.

Mean hemisphere blood flow was calculated from the second slice (orbitomeatal = +5 cm), comprising mainly the occipital, temporal and frontal lobes and the basal ganglia (Tables 4 and 7). Cortical blood flow was calculated in all three slices in selected areas of interest, defined either by the criteria of an asymmetrical flow map, or by relevance to the patients' focal symptoms or headache localization. Basal ganglia blood flow was calculated in patients with common migraine to disclose possible pain-related changes of this region. Symmetrical areas of appropriate size were compared. We defined a significant change of blood flow in these areas to be a difference of more than 10 per cent, a difference not exceeded in any of the 20 normal subjects studied with the same equipment. Student's t test (paired and unpaired) was used for the statistical evaluations.

RESULTS

Patients with Classical Migraine

The medical histories of the patients are given in Tables 1 and 2. (For all Tables *see* Appendix.) The timing of blood flow and symptoms is given in Table 3. The migraine attack on the day of investigation sometimes differed from the habitual ones with regard to focal symptoms and headache localization. The minor discrepancies can be studied by comparing Tables 2 and 3.

Blood flow and symptoms before treatment. The 11 patients were studied at ½ to 3½ h (2 ± 1 h) (mean ± SD) after the onset of the attack. Two were only studied once, 9 repeatedly. In 2 patients (Cases 9 and 11), blood flow changes and symptoms disappeared without treatment in the course of 3 h during five rCBF studies. Another 2 patients (Cases 3 and 4) were studied during prodromes, and again during headache. rCBF changes remained unaltered. In 7 patients, the rCBF pattern and symptoms (mainly mild residual focal neurological disturbances and the migraine headache) were the same in repeated measurements.

Of 11 patients, 8 exhibited significant rCBF abnormalities ½ to 3½ h after their first symptom, while 3 patients who were studied ¾ to 4 h after the onset of the attack did not. A unilateral area of hypoperfusion involving the posterior part of the brain was seen in 7 of 8 cases. The eighth showed only a hypoperfusion of the right frontal lobe. The low blood flow was in all cases confined to the tomographic representation of the cortex, the subcortical structures showing only minor, insignificant blood flow asymmetries. In 7 patients, the reduced flow as observed only on the lateral aspect of the hemisphere, while in 1 (Case 3), the mesial cortex of the occipital region also appeared to be involved (figs. 1 and 2).

The decrease of blood flow was 17 ± 7 per cent (mean ± SD) compared with the corresponding contralateral region. Absolute levels of average rCBF, $PaCO_2$ and blood pressure are given in Table 4. Between individuals, rCBF in the hypoperfused regions varied between 41 and 66 $ml.100g^{-1}.min^{-1}$.

The unilateral cortical hypoperfusion, when present, consistently corresponded to previous or current focal neurological symptoms of the contralateral side of the body. The hypoperfusion remained unchanged in size and intensity in the 2 patients studied at the end of their prodromes and during the development of headache. Headache was the main symptom in the remaining 6 patients with unilateral hypoperfusion; focal symptoms were either slight or absent. Accordingly, hypoperfusion persisted when only mild, if any, focal neurological symptoms were experienced.

Eight patients had unilateral headache while 3 had bilateral headache. Of the former, 6 exhibited low flow at the side of pain, while 2 (Cases 5 and 6) had a symmetrical flow map. Of the patients with bilateral pain, 2 had a unilateral hypoperfusion (Cases 1 and 10), while 1 (Case 2) had a normal symmetrical blood flow distribution.

Blood flow and symptoms after treatment. The post-treatment studies were made in 9 patients (2 had recovered spontaneously) 4½ to 7 h (6 ± 1 h) (mean ± SD) after the onset of attack, when the patients no longer had any symptoms. Blood flow distribution had then normalized in 3 of the 7 patients who had previously exhibited a hypoperfusion, and 2 with a normal symmetrical flow map at the first investigation still had a normal flow pattern. In 2 patients, the size of the hypoperfused region had decreased considerably (Cases 4 and 8), in 1, the size and intensity of hypoperfusion was unchanged (Case 10), while in 2 patients (Cases 1 and 11), regions of hypoperfusion appeared in either or both hemispheres. The usual duration of the hypoperfusion in treated classical migraine attacks therefore appeared to be in the order of 6 h. Mean hemisphere blood flow of the nonaffected side remained the same after treatment with ergotamine and metoclopramide ($P > 0.10$).

Blood flow changes in headache-free period. At re-examination, at least one week after the attack, all but one patient displayed a normal, symmetrical blood flow distribution. In Case 4, the left insula still showed some degree of hypoperfusion.

Patients with Common Migraine

The medical histories of the 12 patients are given in Table 5. In general, patients with common migraine presented at the clinic later in their attacks than those with classical migraine. The time from the onset of headache to rCBF investigation varied between 3 and 20 h (mean 7 ± 5 h). At this time, mean hemisphere and cortical blood flow was normal and symmetrical: hypo- or hyperperfused regions were neither observed ipsi- or contralaterally to the side of pain (fig. 3, Table 6). Blood flow in the basal ganglia, notably in their posterior parts, was calculated to elucidate pain-related activation of this region (Table 7). No attack-related side-to-side asymmetry was seen ($P > 0.10$). No alterations were noted comparing hemisphere or cortical blood flow during attacks to the post-treatment on the same day, or to the study performed days after in a headache-free period (Table 7) ($P > 0.25$).

DISCUSSION

In our previous studies of induced classical and common migraine attacks we followed the initial phases by closely spaced rCBF examinations (Olesen *et al.*, 1981*a*, *b*; Lauritzen *et al.*, 1983*a*). In the present study, measurements were made roughly corresponding to the phase of the attack when they were terminated in the previous series. The fully developed attacks were studied in most cases, when symptoms and cerebral blood flow remained stable for hours until the attack abated.

Classical Migraine

Time course of symptoms and cerebral blood flow changes. The current view of migraine pathophysiology, which is that cerebral vasospasm causes focal ischaemic symptoms while extra- and/or intracranial hyperperfusion accompanies the pain (Wolff, 1963), has recently been contradicted: in studies of induced classical migraine, which allowed investigation of the very first period of the attack, the regional hypoperfusion developed before and outlasted the focal symptoms (hemiparesis/paraesthesiae) (Olesen *et al.*, 1981*a*; Lauritzen *et al.*, 1983*a*). This dissociation in time of perfusion changes and symptoms indicated that the prodromes were not caused by the low flow *per se*. Also in the present study, the hypoperfusion tended to outlast the focal neurological symptoms, as the latter were either attenuated or absent at the time of investigation. The hypoperfusion more probably reflected a disturbance of brain metabolism which also caused the symptoms. The duration of the hypoperfusion was according to the present data usually between 3 and 6 h, but cases of longer duration were also seen. Moreover, it is likely that the hypoperfusion may last less than 4 h or not occur at all. Three patients, 2 with exclusively visual and 1 with visual as well as limb prodromes, did not exhibit any flow changes though they were studied ½ to 3 h after the onset of the attack. Blood flow changes might have disappeared at this time, but manifest classical migraine with insignificant changes of the brain circulation was also observed during the induced attacks in 2 patients in our previous study (Lauritzen *et al.*, 1983*a*).

The average reduction of cerebral blood flow in the hypoperfused regions was only 17 ± 7 per cent and thus above the average decrease of 24 ± 3 per cent reported in our previous study of induced attacks (Olesen *et al.*, 1981*a*; Lauritzen *et al.*, 1983*a*). In the two-dimensional approach to the measurement of cerebral blood flow used in the latter studies, superposition of normally perfused brain tissue, and Compton-scatter from surrounding normal brain, tend to hide small, hypoperfused regions. This results in overestimation of flow in hypoperfused areas (Skyhøj Olsen *et al.*, 1981). In the present study, the tomographic technique circumvented superposition of tissue layers. On the other hand, the higher counting rate instrumental for a good spatial resolution increased Compton-scatter. This may explain the more moderate focal reduction of blood flow in the present study. Because of the technical limitations outlined above, we cannot exclude the possibility of ischaemia in the hypoperfused regions in this or our previous studies.

*Hyper*perfusion was not observed, although the patients were investigated during severe headache. On the contrary, 8 of 11 patients exhibited a unilateral hypoperfusion, 6 ipsilaterally to the side of pain and 3 patients had no flow changes at all. This observation agrees with the results of our previous series of induced classical migraine attacks when 10 out of 12 patients exhibited oligaemia during headache (Olesen *et al.*, 1981*a*; Lauritzen *et al.*, 1983*a*). Thus, cerebral hyperperfusion is not the cause of pain in classical migraine.

'Spreading oligaemia', abnormalities of cerebral blood flow regulation, and localization of persisting hypoperfusion in classical migraine. In induced classical migraine attacks, hypoperfusion developed in a wave-like manner, spreading anteriorly, independently of the territories of supply of large arteries ('spreading oligaemia') (Olesen *et al.*, 1981*a*). The progression rate was close to 2 mm/min. The oligaemia did not cross major cytoarchitectonic borders (the central sulcus) or discontinuity of neurons (the lateral sulcus), but probably reached the frontal lobe by way of the insular region. Thus, frontal oligaemia typically appeared corresponding to the frontal or orbital operculum (Lauritzen *et al.*, 1983*a*). Abnormalities of

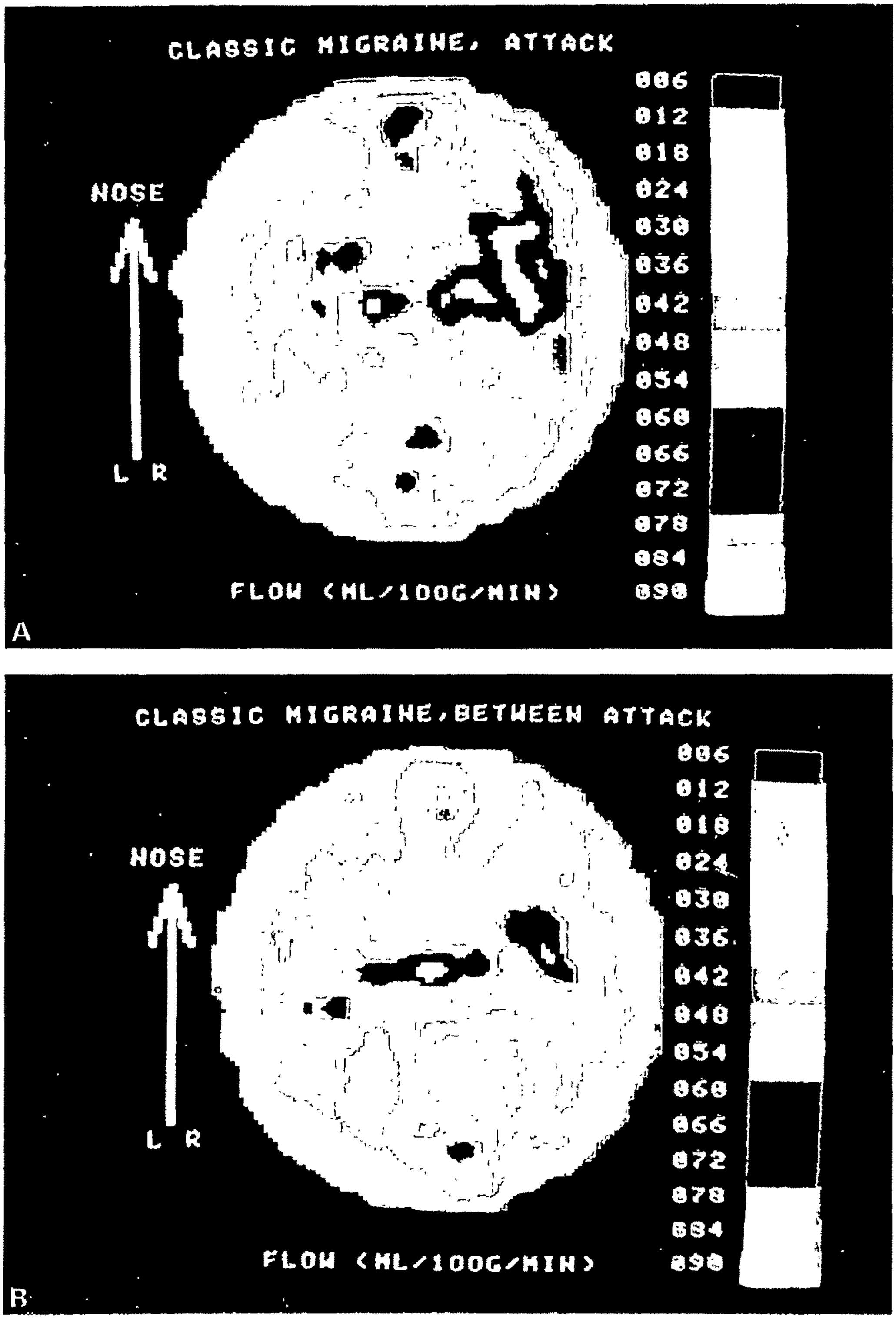

FIG. 1. CBF tomograms of patient with classical migraine (Case 4 in Tables). This 24-year-old woman with familial hemiplegic migraine arrived at the clinic after right scintillations, hemiparesis and aphasia, and suffered at the time of rCBF study from right arm paraesthesiae, left-sided headache, nausea and photophobia. The tomogram 5 cm above the orbitomeatal line shows reduced blood flow corresponding to the tomographic representation of left lateral temporal, parietal and frontal cortex (A). Between attacks, blood flow distribution was normal and symmetrical, except for the left insula which still showed some degree of hypoperfusion (B).

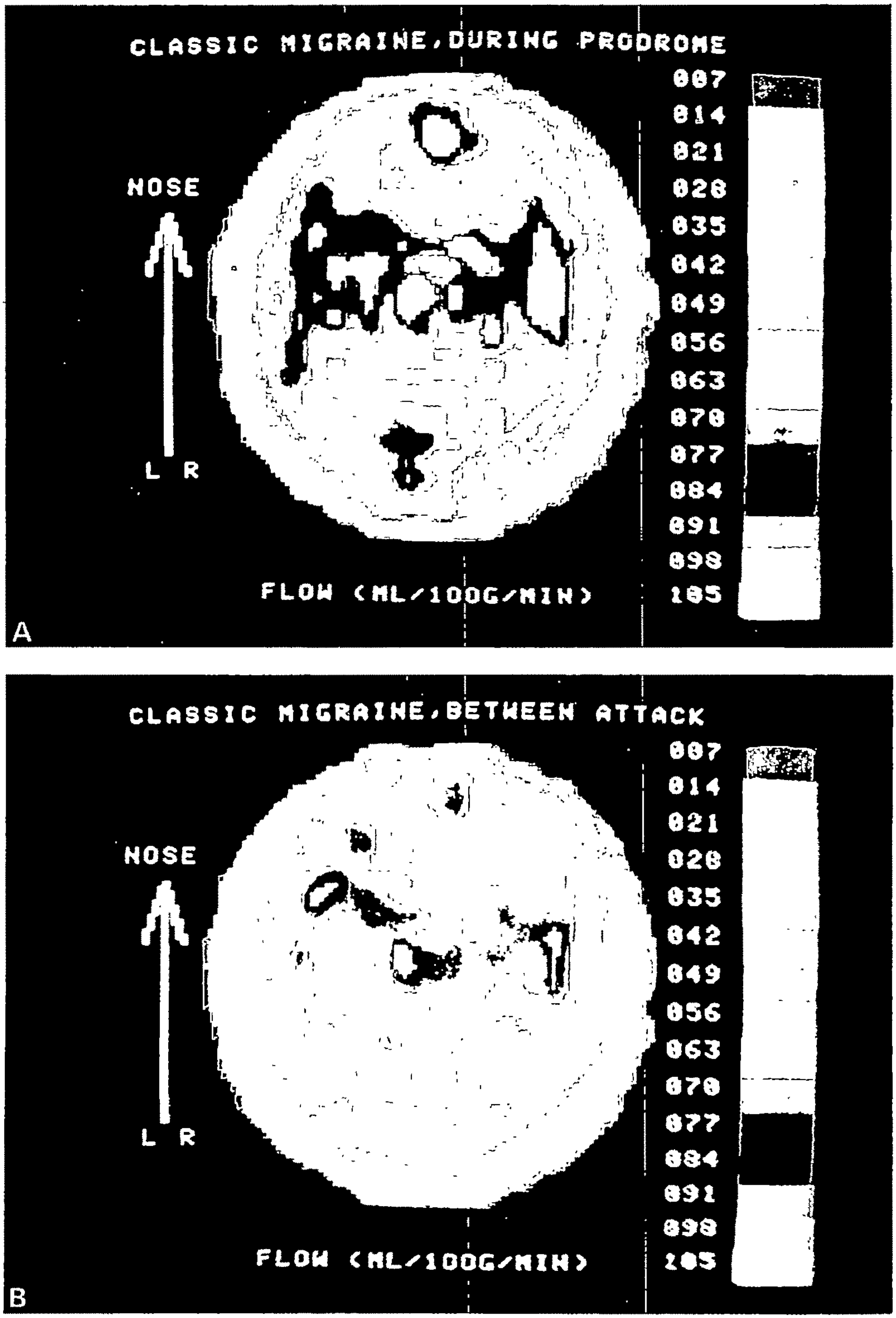

FIG. 2. CBF tomograms of patient with classical migraine (Case 3 in Tables). This 18-year-old man arrived at the clinic when his visual prodromes had almost ended. At time of investigation he exhibited waning left scintillations and a mild right frontal headache. The tomogram 5 cm above the orbitomeatal line showed hypoperfusion corresponding to the tomographic representation of the mesial and lateral right occipital, and lateral right temporal cortex (A). Outside attack, blood flow was normal and symmetrical (B).

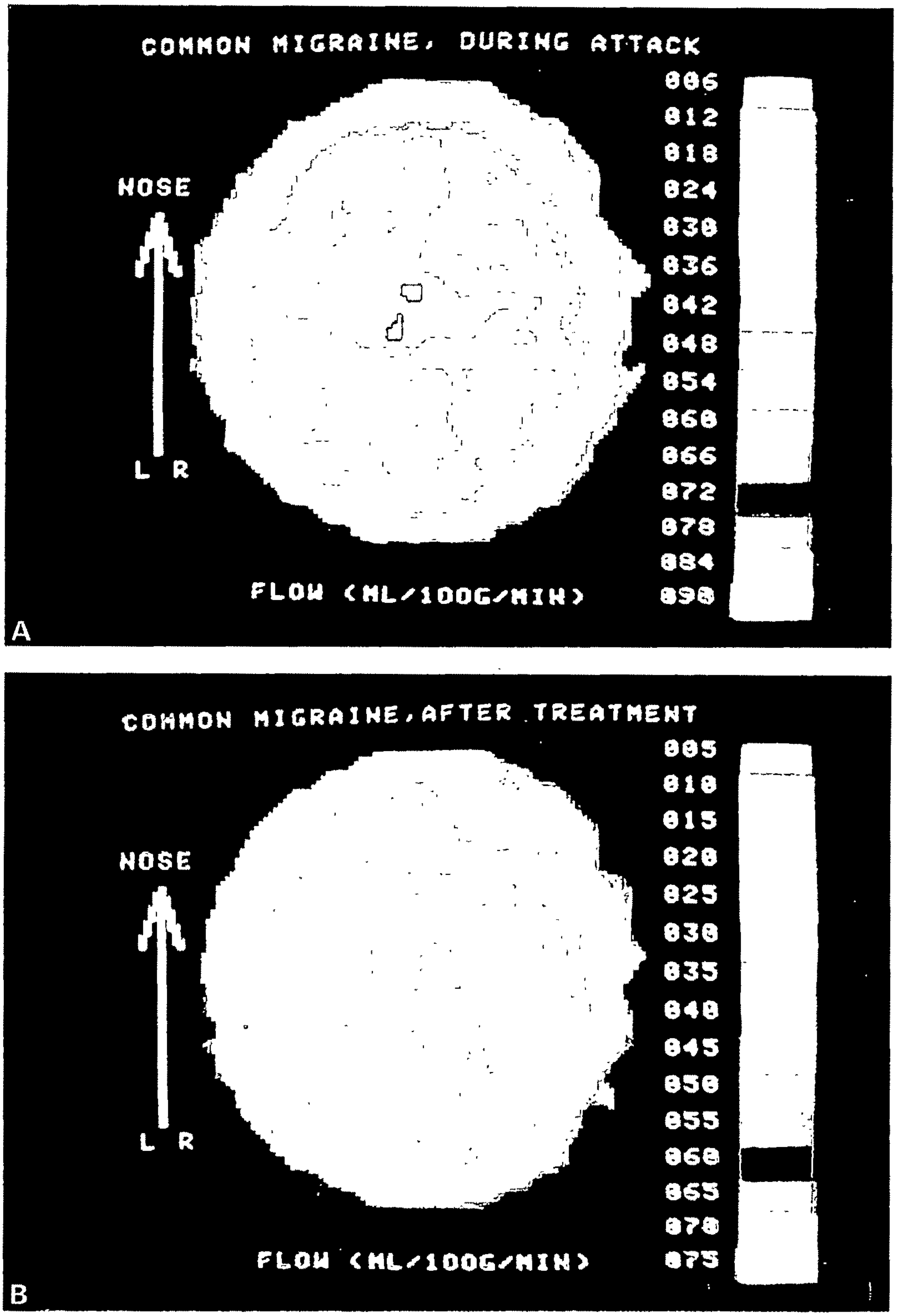

FIG. 3. CBF tomograms of patient with common migraine (Case 6 in Tables). This 42-year-old woman with common migraine arrived at the clinic 7 h after waking up in the morning with right throbbing headache, nausea, vomiting and phono- and photophobia. Symptoms were unchanged at time of investigation. The tomogram 5 cm above the orbitomeatal line showed a normal and symmetrical flow distribution (A). After treatment, blood flow was likewise normal (B).

blood flow regulation consisted of a reduced CO_2 activity, and severely impaired cortical activation, while blood pressure autoregulation was normal. These abnormalities were strictly confined to the hypoperfused regions, while neighbouring normally perfused brain tissue had a normal blood flow regulation (Lauritzen *et al.*, 1983*b*). The present study provided for exact localization of this vasomotor dysfunction: the unilateral hypoperfusion appeared in all cases confined to tomographic representation of the cortex, and in 7 of 8 patients only on the lateral aspect of the hemisphere. Subcortical structures showed a normal, symmetrical blood flow distribution and were accordingly not directly involved in the migraine process. One patient (Case 4) exhibited hypoperfusion of the frontal lobe simultaneously with low flow of the temporal and parietal lobes. In this patient also the insular region was hypoperfused. This observation indirectly supported the suggestion that the insula is the pathway of the 'spreading oligaemia' to the frontal lobe (Lauritzen *et al.*, 1983*a*).

The compiled cerebral blood flow data from the patients with spontaneous and provoked classical migraine attacks make out a characteristic pattern of a slowly spreading, moderate cortical hypoperfusion persisting for hours, probably caused by a local perturbation of vasomotor regulation. We have previously emphasized the similarity between these flow changes and the blood flow changes of the rat brain after Leão's spreading depression (Lauritzen *et al.*, 1982).

Cerebral bloodflow changes of the rat brain in Leão's spreading depression and their possible relevance to 'spreading oligaemia'. Leão's spreading depression (SD) is a transient perturbation of neuronal function which arises as a response of the cerebral cortex to a variety of noxious stimuli (Leão, 1944*a*; Bureš *et al.*, 1974). The rate of spread (3 mm/min) of the brief neuronal burst (5–10 s), followed by the longer lasting depression of EEG (5–10 min), and evoked potentials (up to 1 h), correspond well with the march of sensory disturbances in migraine, as noted already by Leão (Leão and Morison, 1945). Spreading depression is accompanied by marked blood flow changes: at the beginning of the EEG depression, cortical blood flow increases by 100 per cent for 1 to 2 min in a 2 to 3 mm wide band as a consequence of pial vasodilation (Leão, 1944*b*; Hansen *et al.*, 1980). Following this increase, blood flow decreases by 25 to 30 per cent from the baseline for at least 1 h. The observation of the hypoperfusion after spreading depression led us to suggest that 'spreading oligaemia' was an epiphenomenon to spreading depression, occurring in its wake (Lauritzen *et al.*, 1982). The rate and mode of spread of the 'spreading oligaemia' supported this viewpoint. The abnormalities of blood flow regulation of 'spreading oligaemia' consisted of preserved blood pressure autoregulation, reduced CO_2 response and impaired cortical activation to mental tests (Olesen *et al.*, 1981*a*; Lauritzen *et al.*, 1983*b*). In the post-SD period, blood pressure autoregulation was also normal while the CO_2 response was reduced. Metabolic autoregulation still remains to be investigated (Lauritzen, 1983). The similarity of the regulation abnormalities further supported an association between the two phenomena. On the assumption that the persistent cortical hypoperfusion observed in the present study is the consequence of spreading oligaemia, the parallel can be drawn even further since the hypoperfusion after spreading depression was also persistent, and purely cortical (Lauritzen *et al.*, 1982).

Common Migraine

Until a few years ago, only few studies in migraine distinguished clearly between classical and common migraine. This pertains in particular to regional cerebral blood flow studies. Therefore textbooks and reviews have treated migraine as a pathophysiological unit. In fact the symptomatology of classical and common migraine is markedly different, as recognized in current migraine definitions (Ad Hoc Committee, 1962). We therefore expected different flow reactions in the two forms of migraine and confirmed the suspicion of a normal rCBF pattern in common migraine in studies of induced attacks (Olesen *et al.*, 1981*b*). It could be questioned whether the results were also representative of spontaneous attacks. The present study confirmed that a normal flow pattern is the usual finding in common migraine. We estimated the average duration of the cerebral hypoperfusion in classical migraine to be 4 to 6 h. The 12 patients with common migraine were studied at an average of 7 h after the onset of symptoms, 5 patients within the first 4 h. If the attacks were associated with a state of cerebral hypoperfusion similar to classical migraine, we would have observed it, at least in some cases. With the results from both studies of common migraine at hand, we may therefore conclude that the common migraine attack is only infrequently associated with appreciable cerebral oligaemia. Exceptions to this notion are the 3 patients with common migraine, studied with intracarotid rCBF, who exhibited low-flow regions during their induced migraine attacks (Olesen *et al.*, 1981*a*; Gelmers, 1982).

Hyperfusion was not observed at any time of the attacks. This was true for hemisphere as well as for focal flow values. All patients had moderate to severe pain during one or more measurements. It is therefore unlikely that cerebral hyperperfusion is involved in the pain mechanism of common migraine. The difference between our findings and those of previous authors who found a slight but significant increase of rCBF during and after the pain (Skinhøj, 1973; Mathew *et al.*, 1976; Sakai and Meyer, 1978) may be explained by the different timing of rCBF investigations in relation to symptoms, differences between the patients and the very different techniques for rCBF determination.

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APPENDIX

TABLE 1. MEDICAL HISTORY OF PATIENTS WITH CLASSICAL MIGRAINE

Case No.	*Age (yrs)*	*Sex*	*Family history of migraine*	*Duration of history (yrs)*	*Other investigations*
1	23	F	Yes	9	EEG, CT scan and L. carotid arteriography normal
2	26	F	Yes	1	EEG and CT scan normal
3	18	M	Yes	3	None
4	24	F	Yes	18	EEG and CT scan normal
5	25	M	Yes	19	EEG normal
6	52	M	No	25	None
7	41	F	No	24	EEG normal
8	23	M	Yes	12	EEG, CT scan, R. carotid arteriography normal
9	45	M	No	37	None
10	42	M	No	30	None
11	23	F	Yes	9	EEG normal

TABLE 2. CHARACTERISTICS OF USUAL ATTACKS OF CLASSICAL MIGRAINE

Case No.	*Frequency of attacks/yr*	*Duration of attacks (h)*	*Symptoms*
1	2	24	Bilat. scintillations, R. hyp/paraesthesiae for 1 h, preceding and accompanying bilat. pressing headache and photo/phonophobia.
2	—	48	R. scintillations, hyp/paraesthesiae preceding R. pressing headache.
3	2	7	L. scintillations preceding a R. or L. throbbing frontal headache, nausea and photophobia.
4	12	7	R. scintillations, par/hypaesthesia and weakness preceding bilat. pressing headache, nausea and vomiting.
5	12	24	R. or L. scintillations, sometimes followed by corresponding R. or L. paraesthesiae and paresis, preceding bilat. pressing headache, vomiting and phono/photophobia.
6	12	30	Scintillations in both visual fields preceding L. throbbing headache, nausea and photophobia.
7	12	24	R. or L. scintillations followed by corresponding R. or L. arm, face and tongue hypaesthesia and paresis, preceding and accompanying L. or R. throbbing headache, nausea and phonophobia.
8	2	6	Bilat. central scotoma, L. par/hypaesthesiae and paresis preceding uni- or bilat. throbbing headache, phono/photophobia and nausea.
9	4	5	R. or L. scintillations followed by corresponding hand and sometimes face par/hypaesthesia. When R., also aphasia. Then or simultaneously uni- or bilat. throbbing headache.
10	4	9	Bilat. or R. scintillations and scotoma followed by bilat. pressing headache.
11	2	10	R. scintillations and L. arm par/hypaesthesiae and paresis preceding bilat. pressing headache and phono/photophobia.

TABLE 3. REGIONAL CEREBRAL BLOOD FLOW IN CLASSICAL MIGRAINE: TIME RELATION OF BLOOD FLOW DISTRIBUTION TO SYMPTOMS

Case No.	*Time since onset of attack (h)*	*Symptoms during investigation*	*Blood flow distribution*
1	2	Bilat. scintillations terminated 1 h before, then R. hemiparesis/hemianaesthesia and rhythmic 10–20 Hz tremor of the R. hand, discrete aphasia and pain on top of head. Symptoms and blood flow unchanged during 2 following investigations (2½ and 3 h after onset of attack).	Hypoperfusion of lateral L temporal lobe.
	6½	After treatment (no symptoms).	Hyperperfusion of lateral L. temporal lobe.
2	1	R. scintillations, R. arm, tongue and facial paraesthesiae/hypaesthesia terminated 15 min before, then only R. hand paraesthesiae and bifrontal headache. Symptoms and blood flow unchanged in two following investigations (1½ and 2 h after onset of attack)	Symmetrical perfusion.
	4½	No symptoms.	Symmetrical perfusion
3	½	Discrete L scintillations, mild bifrontal headache.	Hypoperfusion of mesial and lateral R. occipital and lateral posterior temporal lobes.
	1	Mild to moderate R. headache.	Hypoperfusion unchanged.
	1½	Moderate R. frontal headache, nausea and photophobia.	Hypoperfusion unchanged.
	7	After treatment (no symptoms).	Symmetrical perfusion.
4	1	R. scintillations, hemiparesis/paraesthesiae and aphasia at start of attack, then only paraesthesiae of R. arm, photophobia.	Hypoperfusion of lateral L temporal, parietal and frontal lobes.
	1½	Paraesthesiae of R. arm, L. headache, photophobia, nausea. Symptoms and blood flow unchanged in one additional investigation (2 h after onset of attack).	Hypoperfusion unchanged.
	7	After treatment (no symptoms).	Hypoperfusion of L. insula region.
5	¾	L. scintillations terminated ½ h before. Then, R. headache, nausea, photophobia. Symptoms unchanged in two following investigations (1 and 1½ h after onset of attack).	Symmetrical perfusion.
	5½	After treatment (no symptoms).	Symmetrical perfusion.
6	3	Bilat. scintillations terminated 2 h before. Then, L. headache, nausea, photo/phonophobia. Symptoms unchanged in the following measurement (3½ h after onset of attack).	Symmetrical perfusion.
	7½	After treatment (no symptoms).	Symmetrical perfusion.
7	3½	L. scintillations, tongue, throat and facial paraesthesiae terminated 1–2 h before. Then only L. hand par/hypaesthesiae, light R. headache. Symptoms and blood flow unchanged in one additional investigation (4 h after onset of attack).	Hypoperfusion of lateral R. frontal lobe.
	6½	After treatment (no symptoms)	Symmetrical perfusion.
8	3	L. scintillations, mild hemiparesis/paraesthesiae, R. headache, and photo/phonophobia	Hypoperfusion of lateral R. occipital temporal and parietal lobes.
	4½	After treatment (no symptoms).	Hypoperfusion of lateral R. temporal pole.
9	2½	Predominantly R. scintillations terminated 1½ h before, R. hand paraesthesiae and aphasia in remission, slight L. pressing headache.	Hypoperfusion of lateral L. temporal lobe.
	5	After spontaneous recovery.	Symmetrical perfusion.
10	3	Bilat. scintillations terminated 2½ h before, then diffuse, bilat. pressing headache, nausea and photophobia.	Hypoperfusion of L. temporal lobe.
	5	After treatment (no symptoms).	Hypoperfusion unchanged.
11	1½	R. scintillations terminated 1 h before, L. arm paraesthesiae and slight bilat. pressing headache.	Hypoperfusion of lateral L. parietal cortex and R. temporal pole.
	2	L. arm paraesthesiae in remission, bilat. pressing headache, phono/photophobia.	Hypoperfusion unchanged.
	6	After spontaneous recovery.	Hyperperfusion of L. occipital, and R. temporal and frontal lobes.

The terms hypo- and hyperperfusion refer to statistically significant differences in flow between the two hemispheres, i.e. a difference of 10 per cent or more between symmetrical brain regions.

TABLE 4. rCBF IN CLASSICAL MIGRAINE: ABSOLUTE VALUES IN REGIONS OF INTEREST

		Hemisphere CBF		*CBF in cortical areas of interest*												
				Total cortex		Occipital		Parietal		Temporal		Frontal		Cerebellar mean flow		
Case No.	CBF No.	L.	R.	L.	R.	L.	R.	L.	R.	L	R	L	R.		MABP (mm Hg)	PaCO$_2$ (mm Hg)
		CBF (ml/100 g/min)														
1	a	52	57	46	57	54	54	55	55	46	53*	56	56	74	100/85	40.3
	b	64	62	62	60	78	77	69	69	69	54*	58	57	74	110/90	36.7
	c	56	56	56	57	56	56	59	59	55	55	53	50	67	110/90	36.0
2	a	59	59	57	57	57	52	64	61	53	57	58	59	48	100/70	33.8
	c	68	68	67	67	77	75			64	60	64	65	71	105/70	39.0
3	a1	72	68	71	66	66	54*	72	66	71	61*	69	66	68	130/80	41.0
	a2	64	59	63	57	59	49*	67	66	57	45*	60	61	64	130/70	36.7
	a3	63	59	60	57	60	53*	66	69	59	49*	61	63	64	120/60	35.3
	b	54	54	54	55	58	55	59	59	49	53	51	49	64	145/70	35.3
	c	58	57	59	58	59	57	58	57	53	52	57	56	55	130/60	35.3
4	a1	51	57	46	57	47	50	52	59*	42	50*	42	62*	62	110/80	34.6
	a2	49	61	50	61	53	58			50	60*	41	63*		140/70	33.8
	b	52	53	52	54	54	50	55	54	59	58	50	54	59	115/80	38.2
	c	49	49	47	50	46	46	53	52	54	54	50	51	57	115/80	33.1
5	a	50	48	51	48	50	48			49	46	51	50	49	140/75	27.4
	b	48	48	47	48	51	48			47	43			56	145/90	30.0
	c	48	47	46	46	45	50			42	43	49	44	42	140/90	31.0
6	a	66	63	58	53	53	48	69	65	55	53	62	64	61	130/85	36.7
	b	62	59	58	57	55	50	57	55	47	46	63	58	75	110/80	35.3
	c	63	61	61	62	56	52	70	64	54	54	64	63	65	120/85	34.6
7	a	53	54	54	53	61	62	52	49			62	52*	60	110/85	31.7
	b	55	56	51	54	56	58	51	49			59	56	58	125/90	34.6
	c	52	49	50	50	47	49	51	49			54	53	47	120/85	32.4
8	a	58	53			53	45*	53	45*	61	52*	59	58	72	120/80	37.4
	b	60	57	56	52	57	52	59	57	63	52	62	57	70	120/80	38.9
	c	66	66	62	62	70	64	68	69	58	62	69	63	83	130/90	38.9
9	a	50	51	50	52	52	48	51	52	48	54*	49	51	51	130/90	30.4
	b	58	51	60	56			62	57			58	54	60	130/90	34.2
	c	50	51	51	51	51	49	48	47	49	50	55	54	53	130/90	30.2
10	a	57	58	57	60			55	57	51	58*	59	61		115/75	36.0
	b	56	59	56	59			53	54	52	60*	58	61		115/75	36.0
	c	60	60	60	63			58	59	60	63	53	56		115/85	34.6
11	a1	49	50	49	50	50	46	44	52*	53	46*	49	48	53	115/85	23.0
	a2	52	52	51	51	52	49	44	49*	61	55*	54	53	71	120/80	23.0
	b	74	74	74	76	83	71*			66	72*	73	80*	68	100/65	32.4
	c	62	63	63	65	67	65	57	60	60	54	64	65	58	100/65	31.7

The lower case letters of the second column refer to rCBF studies before (a) and after (b) treatment with ergotamine and metoclopramide, and in a headache-free period (c). The numbering of the investigations before treatment in Cases 3, 4 and 11 refer to successive examinations during the attack, when a change of symptoms occurred. *Statistically significant differences of flow between symmetrical brain regions

TABLE 5. MEDICAL HISTORY OF PATIENTS WITH COMMON MIGRAINE

Case No.	Age (yrs)	Sex	Family history of migraine	Duration of history (yrs)	Frequency of attacks/yr	Usual duration of attacks (h)	Usual localization and quality of headache	Usual associated symptoms				
								Nausea	Vomiting	Diarrhoea	Photophobia	Photopsiae
1	59	F	Yes	40	12	36	Rt. pressing	Yes	Yes	No	Yes	Never
2	54	F	Yes	22	12	12	Bitemporal throbbing	Yes	Yes	Yes	Yes	Sometimes
3	62	F	Yes	42	18	30	L. or R. pressing	Yes	Yes	Yes	Yes	Sometimes
4	39	F	No	22	4	14	R. pressing	Yes	Yes	No	Yes	Never
5	36	F	No	10	24	24	L. or R. throbbing	No	No	No	Yes	Never
6	42	F	No	6	24	60	R. pressing	Yes	Yes	No	Yes	Never
7	40	F	No	26	18	18	R. throbbing	Yes	No	No	Yes	?
8	35	M	Yes	12	30	—	R. throbbing	Yes	Yes	Sometimes	Yes	Never
9	35	F	Yes	5	30	36	L. throbbing	Yes	Yes	No	Yes	Sometimes
10	29	F	No	9	18	24	L. or bilat. throbbing	Yes	Yes	No	Yes	Never
11	38	F	No	3	2	Unknown	Bilat. pressing	Yes	No	Yes	Yes	Never
12	52	F	No	36	5	48	Bifrontal throbbing	Yes	Yes	No	Yes	Never

TABLE 6. rCBF IN COMMON MIGRAINE: SYMPTOMS OF ACUTE ATTACK AND BLOOD FLOW DISTRIBUTION

Case No.	Time since onset of attack (h)	Pain			Associated symptoms				Blood flow distribution
		Localization	Quality	Intensity	Nausea	Vomiting	Diarrhoea	Photophobia	
1	3	Bioccipitally and R. temple	Pressing	3	Yes	Yes	No	Yes	Normal
2	10	Bilat.	Throbbing	3	Yes	Yes	No	Yes	Normal
3	10	R.	Pressing	3	Yes	Yes	Yes	Yes	Normal
4	8	R.	Throbbing	2	Yes	Yes	No	Yes	Normal
5	4	L.	Pressing	2	Yes	Yes	No	Yes	Normal
6	7	R.	Pressing	3	Yes	Yes	No	Yes	Normal
7	6	R.	Throbbing	2	Yes	No	Yes	Yes	Normal
8	4	R.	Throbbing	2	Yes	No	No	Yes	Normal
9	20	L.	Pressing	2	Yes	No	No	Yes	Normal
10	4	R.	Throbbing	2	Yes	No	No	Yes	Normal
11	8	Bilat.	Throbbing	2	Yes	No	No	Yes	Normal
12	3	Bifrontal	Throbbing	3	Yes	No	No	Yes	Normal

The intensity of the headache was evaluated on a four-point verbal pain scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

TABLE 7. rCBF IN COMMON MIGRAINE: ABSOLUTE LEVELS IN REGIONS OF INTEREST

		Hemisphere CBF (ml/100 g/min)		*Regional CBF (ml/100 g/min)*					
				Total cortex		*Basal ganglia*			
Case No.	*CBF No.*	*L.*	*R.*	*L.*	*R.*	*L.*	*R.*	*Blood pressure (mm Hg)*	*$PaCO_2$ (mm Hg)*
1	a	78	76	75	72	91	88	115/80	38.9
	b	76	75	75	76	96	86	—	44.6
	c	60	60	61	61	—	—	110/80	35.8
2	a	87	88	80	79	98	94	190/90	45.0
	b	84	92	84	97	—	—	160/90	43.9
	c	64	64	62	63	73	71	150/70	40.3
3	a	51	54	51	51	58	58	120/90	33.1
	b	49	48	49	49	55	53	125/90	—
	c	61	59	61	60	74	73	115/90	40.3
4	a	75	72	74	71	80	77	160/100	36.0
	b	65	65	62	63	81	75	—	41.8
	c	59	56	57	54	63	61	135/95	34.6
5	a	51	49	49	45	61	49	140/80	33.1
	b	57	54	56	51	68	67	—	37.4
	c	—	—	—	—	—	—	—	—
6	a	59	58	56	56	71	66	110/80	37.8
	b	46	44	44	41	56	55	—	40.3
	c	64	64	61	62	77	70	—	34.6
7	a	61	61	58	63	81	73	160/100	—
	b	58	56	58	55	61	57	115/80	31.0
	c	—	—	—	—	—	—	—	—
8	a	49	46	48	48	58	52	140/80	28.8
	b	62	63	62	64	65	62	140/100	39.6
	c	—	—	—	—	—	—	—	—
9	a	55	55	53	53	66	65	100/60	28.8
	b	59	59	58	59	65	64	—	31.7
	c	73	74	71	72	87	81	95/60	36.0
10	a	77	76	78	70	91	87	120/90	45.0
	b	68	64	69	67	—	—	—	—
	c	66	66	67	65	—	—	—	36.7
11	a	76	75	75	74	85	82	—	42.5
	b	76	68	76	68	83	83	—	42.4
	c	65	62	63	60	77	79	110/80	39.6
12	a	69	66	68	62	84	79	130/80	27.4
	b	61	59	63	60	78	65	130/80	29.5
	c	55	52	54	50	60	55	130/90	31.7

The lower case letters of the second column refer to rCBF studies before (a) and after (b) treatment with ergotamine and metoclopramide, and in a headache-free period (c).

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A TWO-ROUTE MODEL OF SPEECH PRODUCTION

EVIDENCE FROM APHASIA

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SUMMARY

Quantitative investigations of speech production deficits are reported in three aphasic patients. Two had impaired paraphasic performance in repetition tasks but relatively well preserved spontaneous speech (conduction aphasia). The other patient had impaired paraphasic spontaneous speech but intact repetition (transcortical motor aphasia). In repetition tasks which required active semantic processing the conduction aphasics were facilitated and the transcortical motor aphasic impaired; in tasks which required passive repetition the opposite pattern of dissociation was observed. These findings are accounted for within a two-route model of the speech production process.

INTRODUCTION

Speech production deficits are frequently observed in aphasic syndromes. Although muscular functioning may be entirely normal, articulation may appear to be effortful and difficult for the patient to initiate with frequent phonemic (literal) paraphasic errors. Such speech production deficits are commonly observed across a wide range of language tests (e.g. in Broca's aphasia). However, in two classical aphasic syndromes there is a striking dissociation between speech production deficits in repetition (imitation) tasks and in spontaneous speech.

The cardinal feature of conduction aphasia is a severe and disproportionate deficit on repetition tasks in the context of intact comprehension and relatively normal spontaneous speech. The conduction aphasic not only has difficulty in repeating lists of digits and words (the production of the individual items being entirely satisfactory) but repetition of polysyllabic words may also be characterized by phonemic paraphasic errors (Goodglass and Kaplan, 1972). The converse pattern of deficit is observed in one subtype of transcortical motor aphasia (Goldstein, 1948); speech production in repetition tasks may be excellent yet spontaneous speech is difficult to initiate, effortful, and has a high incidence of phonemic paraphasic errors (Benson, 1979).

A widely held interpretation of conduction aphasia (Geschwind, 1973) attributes the patient's disproportionate difficulty on word repetition tasks to a disconnection between the areas responsible for speech comprehension (Wernicke's area) and speech production (Broca's area) due to a lesion of the arcuate fasciculus. However, this model is incomplete insofar as it fails to give an adequate account of the relative preservation of spontaneous speech. Other writers have resolved this paradox by postulating a single deficit at the level of output processing which is compensated for by circumlocution (Dubois *et al.*, 1964). There is no satisfactory contemporary interpretation of the subtype of transcortical motor aphasia in which word production in spontaneous speech is impaired but repetition is intact. An alternative and earlier model of these types of aphasia would appear to be more satisfactory. On the basis of clinical observation, Lichtheim (1885) suggested a two-route model such that repetition could be impaired by damage to a route between auditory images of words and motor images of words, although spontaneous speech could still be mediated *via* a route between concept centres and motor images of words. He interpreted transcortical motor aphasia in complimentary terms, namely, as a consequence of the selective impairment of the route between concept centres and the centres for motor images of words.

This early two-route account of speech production deficits has its parallel in recent theoretical models of certain acquired dyslexic syndromes. It is now widely accepted that oral pronunciation of the written word can be achieved in two different ways, either *via* phonological correspondences or by direct access from the semantic system. One consequence of damage to the phonological route is the inability to read nonwords as compared with certain classes of real words (Beauvois and Dérouesné, 1978). This dissociation has recently been discussed with reference to impairment on repetition tasks (Morton, 1980). Furthermore, semantic reading errors are commonly observed in patients with damage to the phonological route and this type of error has now been reported in conduction aphasia (*see* Michel, 1979).

Our aim in this investigation was to explore and test the two-route model for speech production using quantitative techniques. We describe two patients in whom there was a very marked deficit of speech production in repetition tasks but whose spontaneous speech was relatively well preserved, and one patient in whom the opposite pattern of deficits was observed. In a series of experiments, tasks which required semantic processing favoured the two conduction aphasics whereas tasks which minimized the semantic component favoured the transcortical motor aphasic.

CASE REPORTS

Case 1. Conduction Aphasia

O.R.F., a 59-year-old left-handed farmer, was admitted to Chelmsford Hospital on November 10, 1981. He had developed a sudden right-sided headache whilst driving and had collided with some cars on his left. On examination his blood pressure was 200/105, subsequently stabilizing at 130/80. His speech was abnormal, he had left-sided sensory inattention, a left hemiplegia and a left homonymous hemianopia. His CSF was bloodstained and yellow. Bilateral carotid angiography revealed displacement of the right anterior cerebral artery to the left, together with stretching and distortion of

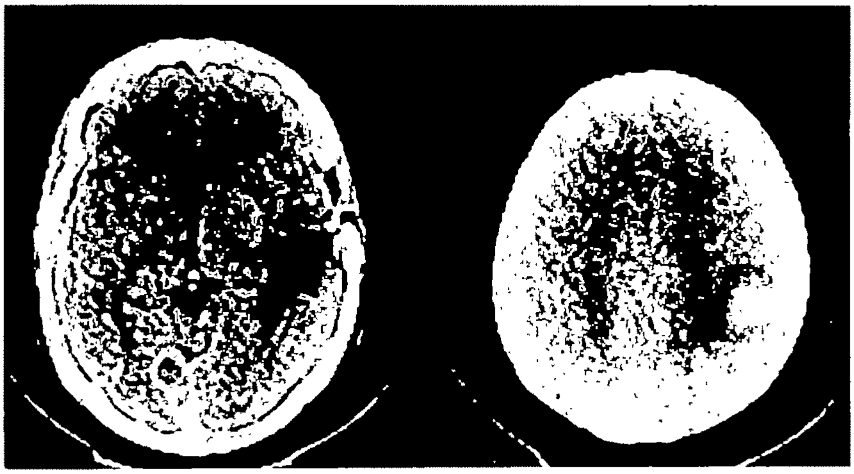

FIG. 1. *O.R.F.* Post-operative scan showing residual low attenuation from the evacuation of a right parieto-temporal haematoma and also a high attenuation lesion in the posterior parietal area prepresenting a more recent haemorrhage.

the temporoparietal branches of the right middle cerebral artery and medial displacement of the sylvian and thalamostriate arteries. The diagnosis of an intracerebral haematoma was made. His condition deteriorated and he became confused. He was transferred to the National Hospital on November 20, 1981 under the care of Dr P. Rudge. The CT scan showed a haematoma of mixed density suggesting repeated haemorrhage which was most dense in the right parietal cortex and extended into the capsular region (*see* fig. 1). Emergency decompression was carried out by Mr D. Thomas two days later; 50 ml of soft haematoma was evacuated together with a second solid haematoma.

He made a satisfactory recovery from craniotomy. On examination on November 23, 1981 it was noted that his speech was paraphasic and that he had extreme difficulty with word repetition. He was referred to the Psychology Department for more detailed assessment on December 2, 1981 and he was seen frequently until his discharge on December 23, 1981.

O.R.F. was assessed on the WAIS on December 2, 1981. He obtained a verbal IQ of 99 and a performance IQ of 92. His subtest scores are shown in Table 1. His responses to the vocabulary and similarities subtests are generally good and there were few instances of phonemic distortion of words. His competent scores on WAIS tests of expressive language function contrast with his extremely poor performance on the digit span subtest. O.R.F. was quite unable to repeat three digits forwards.

O.R.F. had a fairly marked nominal dysphasia. On the McKenna and Warrington (1983) Graded Naming test he was only able to score 3/30. His errors were predominantly circumlocutions and verbal paraphasias (semantic approximations). In addition there were a few examples of literal paraphasia (phonemic errors) and of *conduit de l'approche*. On the Coughlan and Warrington (1978) Naming from Description test he scored 6/15 and on their shortened Token test he scored 5/15. Both these scores are very weak. By December 22, 1981 his nominal aphasia had improved and he was able to name 8/30 objects on the Graded Naming test and 11/15 on the Naming from Description test. The pattern of his errors was very similar to that observed previously.

O.R.F. had a severe dysgraphia and was unable to spell or write even the simplest words on the Schonell test. (His dysgraphia is described in detail by Baxter and Warrington, 1983.) On the Schonell (1942) Graded Word Reading test he scored 66/100 and on the National Adult Reading test (NART) 20/50 (Nelson, 1983). Although these latter two scores are at a satisfactory average level, some of his responses were typically dyslexic.

Although his digit span was very short his ability to articulate individual numbers was satisfactory. However, he had very much more difficulty in articulating two and three syllable words in a repetition task. Thus although he was able to read 20/50 words from the NART he could only repeat 10 and had marked difficulty in repeating a selection of three syllable words from the Schonell spelling test. The clinical impression was that he made far more phonemic (literal) paraphasic errors in repetition tasks than in his spontaneous speech. His memory skills were assessed using the Warrington (1984) Recognition Memory tests. He obtained a defective score on the visual version (24/50) but was at the lower limits of normal on the verbal version, scoring 40/50.

In summary, O.R.F. showed a cluster of language deficits which are typically associated with dysfunction of the posterior areas of the dominant hemisphere. He was dyslexic, dysgraphic and had a slowly resolving nominal aphasia. His performance on repetition tasks was severely impaired as a consequence of two deficits; his digit span was reduced and he made phonemic errors in the production of single polysyllabic words. In contrast he showed relative preservation of his spontaneous speech.

TABLE 1. AGE-SCALED WAIS SUBTEST SCORES

	O.R.F	*R.A.N.*	*A.R.T.*	
	2.12.81	*22.2.83*	*14.9.82*	*25/26.10.82*
Arithmetic	10	4	3	4
Similarities	11	7	5	9
Digit Span	1	1	2	6
Vocabulary	15	6	0	9
Picture Completion	10	9	12	12
Block Design	7	7	6	12
Picture Arrangement	6	10	10	10

Case 2. Conduction Aphasia

R.A.N. was a 51-year-old right-handed plumber. He was admitted to the National Hospital, Maida Vale, under the care of Dr P. Rudge on January 12, 1982 as an emergency, having developed a speech disturbance and loss of the use of his right side over a period of 12 h. On examination he was found to have a flaccid right hemiparesis, a right hemianopia and an extensor plantar response on the right. He was observed to have some difficulty with language comprehension and expression. The CT scan showed a left intracerebral haematoma with compression of the left lateral ventricle. Four vessel angiography (January 13) showed spasm of the proximal part of the anterior temporal branches of the left middle cerebral artery and shift of the internal cerebral veins to the right. No aneurysm was visualized and there was no evidence of any intracranial abnormality on the right. No cause was found for his intracerebral haematoma and he was treated conservatively. He received regular physiotherapy and speech therapy as an outpatient. In April 1982 he developed focal epilepsy which was controlled by phenytoin and in November 1982 he became depressed and was treated with flupenthixol. He was readmitted to the National Hospital, Maida Vale, on January 16, 1983 because of an increase in the frequency of his epileptic attacks. His most recent CT scan (November 1982) showed a large area of low attenuation in the left parietal region which was consistent with an old infarction (*see* fig. 2). On admission he was noted to have a mild right pyramidal weakness, sensory loss on the right and a right extensor plantar response. He was still dysphasic. He was referred to the Psychology Department, National Hospital, Queen Square, for assessment just before his discharge home on February 23, 1983 and it was only possible to see him twice (February 22 and 23).

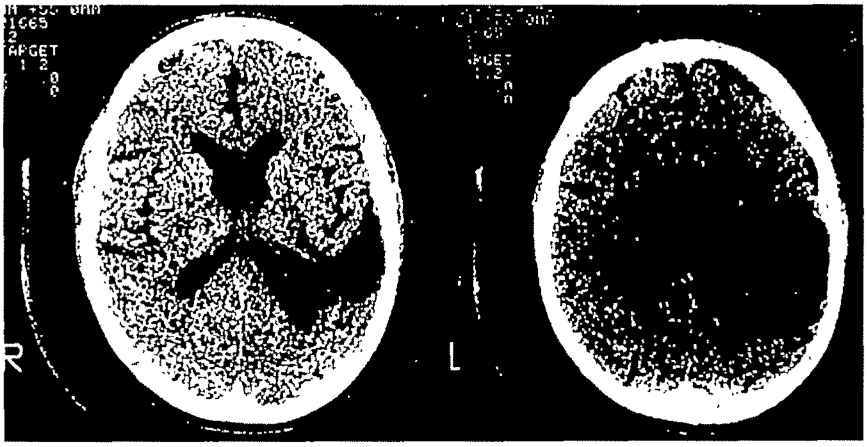

FIG. 2. *R.A.N.* CT scan showing large left parietal region of low attenuation from infarction (the left hemisphere is shown on the right side of this scan).

R.A.N. was assessed on the WAIS on February 22, 1983. His subtest scores are given in Table 1. On verbal subtests although he had clear word-finding difficulties no phonemic paraphasic errors were noted. His digit span was reduced to 2 items. On a recognition memory test for faces his performance was above average (47/50). On a comparable test of recognition memory for words he scored just within normal limits (38/50) which is also very satisfactory considering his language difficulties (Warrington, 1984). He read 40 words from the Schonell Graded Word Reading test and 4 words from the NART. His errors included regularizations of irregular words and phonemic paraphasias.

He was extremely dysgraphic and unable to spell aloud or write any words from a graded difficulty spelling test (Baxter, 1982). On a Graded Naming test (McKenna and Warrington, 1983) his performance was extremely poor (2/30). He made both phonemic and semantic paraphasic errors. On a test of phoneme perception (Coughlan and Warrington, 1978) which requires the sequential comparison of words, he scored 36/40 which is at the lower limits of normal. On the Peabody Picture Vocabulary test he scored 102/150 which is equivalent to an IQ of 91 and is in good accord with his performance IQ. His single word repetition especially for polysyllabic low frequency words was characterized by phonemic paraphasic errors.

R.A.N.'s performance on language tests was somewhat more impaired than O.R.F.'s but he also showed the two cardinal features of conduction aphasia, namely, a severely impaired short-term memory and a speech production deficit in repeating single polysyllabic words in the context of relatively preserved spontaneous speech.

Case 3. Transcortical Motor Aphasia

A.R.T. was a 58-year-old right-handed art school lecturer with a past medical history of intermittent claudication, hypertension, untreated hyperglycaemia and hyperlipidaemia. He had felt well until August 15, 1982 when he became ill with vomiting. Over the course of the following three days he noted blurring of vision and had a headache in the right temporal area. On August 20, 1982 his right arm and leg gradually became weak, and he noticed difficulty with speech production and comprehension. Following a visit to his general practitioner he was admitted to the National Hospital as an emergency under the care of Dr C. J. Earl on August 22, 1982.

On examination he was dehydrated and had a blood pressure of 190/90. The blood glucose level was raised (26.4 mmol/l), as was the plasma urea concentration (9.2 mmol/l). There was evidence of left ventricular hypertrophy, a right carotid bruit, and there were no distal pulses in the lower limbs. He had neglect of the right upper quadrantic field and there was a pyramidal distribution of right-sided weakness with brisk reflexes and increased tone. The CT scan showed an area of low attenuation in the left parietal area consistent with middle cerebral territory infarction (*see* fig. 3). Bilateral angiography showed an acute left internal carotid occlusion. The right vertebral artery was not visualized and may also have been occluded. The diagnoses of left parietal infarction, left internal carotid artery occlusion, hypertension, and diabetes mellitus were made. A.R.T. remained an inpatient at the National Hospital until November 16, 1982, during which time he received intensive speech and occupational therapy. On discharge he was capable of adhering to a suitable diabetic diet and of injecting himself with insulin.

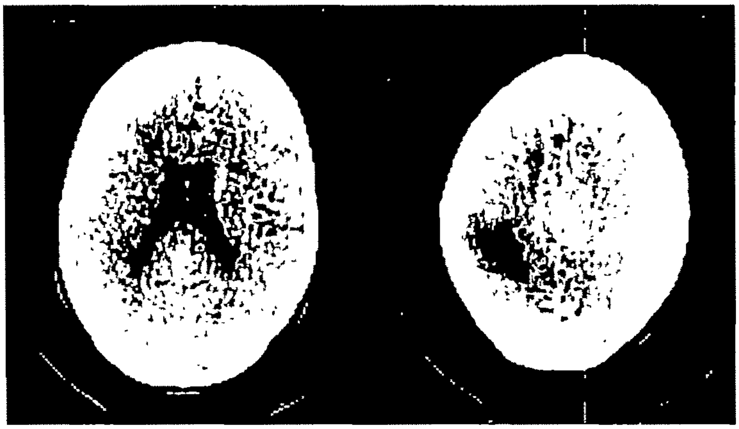

FIG. 3. *A.R.T.* CT scan showing area of low attenuation in the left parietal area from infarction.

He was first assessed on a shortened form of the WAIS on September 14, 1982 and reassessed on October 25 and 26, during which time there had been a significant improvement in both his verbal and nonverbal skills. His subtest scores are shown in Table 1.

On September 14 he was only able to give one answer on the Similarities subtest and made one correct response on Arithmetic. His attempts to respond to Vocabulary items were uninterpretable. On the Digit Span subtest he was able to repeat 4 items forward and there was no evidence of phonemic distortion of individual digits. He was unable to reverse even 2 digits. By October 26 there had been a general improvement in his speech production skills. He was now able to score at a low average level on the Vocabulary and Similarities subtests of the WAIS but the quality of his responses was patchy.

On September 14, 1982 he indicated recognition of 17/20 items on the Unusual Views test of perception and on a test of spatial perception (Position Discrimination) he scored 18/20. These findings indicate intact spatial and perceptual skills. He was given a simple test of recognition memory on this date (Forced-Choice Pictures, J. Willison, personal communication) on which he scored 28/30. His errors appeared to be due to lapses of attention rather than to memory failure. On October 26, 1982 he was given more stringent recognition memory tests (Warrington, 1984). His score on the verbal version was at the lower limits of normal for his age (40/50) and his score on the visual version was above average (45/50). A.R.T. was severely dysgraphic and was unable to spell even the most simple words on the Schonell test.

He was unable to score on the Graded Naming test (McKenna and Warrington, 1983) making frequent phonemic distortions of the target which he attempted to correct. By October 26, there had been a very significant improvement and he now scored 21/30, although he still made a number of phonemic paraphasic errors. This suggests that his optimum score on this test would have been even higher. Informally, A.R.T.'s receptive language skills appeared to be relatively more preserved than his expressive abilities. On the Peabody Picture Vocabulary test (PPVT form a) he scored 123 (IQ equivalent 114). Form b of the PPVT was administered using written presentation and he obtained a score of 130 (IQ equivalent 120). However, A.R.T. appeared to have a selective difficulty in the comprehension of shape names (circle, square and triangle). His complete failure on a modified version of the Token test (0/15) was attributed to this deficit.

In contrast to his good comprehension vocabulary for both the written and spoken word, A.R.T. had a very marked speech production deficit. His spontaneous speech was halting and effortful and his errors were predominantly phonemic distortions as was noted on naming tasks; occasional phonetic distortion was also observed.

He was only able to read aloud 4 common words from the Schonell reading test. His reading aloud like his spontaneous speech was slow and extremely effortful and his errors for the most part were phonemic paraphasias (e.g. 'frog'→'cog'). Although A.R.T. was unable to produce short, high frequency, monosyllables in speech or reading aloud, his repetition of polysyllabic words was prompt and virtually error-free. By October 26, 1982 he was able to produce 46 words correctly on the Schonell test although his errors once again were predominantly phonemic paraphasias (e.g. 'smoulder'→ 'snow-bar'). He was unable to read nonsense words. A very high incidence of phonemic (and occasionally phonetic) distortions occurred in A.R.T.'s expressive speech and reading, which was entirely absent in repetition tasks.

In summary, A.R.T. presented with a severe speech production deficit. His comprehension of written and spoken single words was excellent and his ability to repeat was significantly better than his ability to produce words in reading, naming or spontaneous speech. A.R.T.'s pattern of deficit conforms very closely to that of transcortical motor aphasia.

RESULTS

The dissociation of these patients' abilities in repetition tasks and in spontaneous speech were the subject of the following experimental investigations. We report our experiments with the two conduction aphasics separately from those with the transcortical motor aphasic (even though there is some overlap in procedure) in order to aid clarity of exposition.

A common procedure was used for presentation and recording of all tasks. Material was presented by one experimenter and simultaneously recorded in broad phonemic transcription by the other. Responses were also recorded on cassette tape as a check for the accuracy of transcription. The fidelity of the tape recording was insufficient to permit fine grained analyses of the phonetic characteristics of the patient's speech production.

Experimental Investigations of Conduction Aphasia

Experiment 1: Single Word Repetition and Reading: Frequency and Syllable Length

In this experiment the effects of word frequency and syllable length on O.R.F.'s and R.A.N.'s speech production were documented.

Procedure. Lists of words were prepared using the Thorndike-Lorge Frequency count. There were 90 words in each of two frequency bands: high frequency (A or AA) and low frequency (< 10) (*see* Appendix 1). Thirty words of each set were one syllable, 30 were two syllables and 30 were three syllables long. Phonemic complexity (e.g. the presence of consonant clusters) was approximately balanced across the six (frequency x syllable length) conditions. O.R.F. was required to repeat and to read these word lists, the conditions were presented in an ABBA design. R.A.N. was only tested in the repetition condition. Presentation of single words for repetition was pseudorandomized across frequency and length conditions. The patients were required to repeat each word immediately after stimulus presentation: words were presented following a 5 s interval from the patient's response. In reading single words O.R.F. read across the page on which items were printed in columns: on each line low frequency words were read first, followed by high frequency words. In each frequency condition syllable length increased across columns. He was instructed to take his time when reading. O.R.F. attempted this task twice, first on December 11 and subsequently on December 14, 1981. R.A.N. performed the repetition task on one occasion only (February 23, 1983).

TABLE 2. SINGLE WORD REPETITION AND SINGLE WORD READING: PERCENTAGE CORRECT

		Syllable length		
	Frequency	*1*	*2*	*3*
O.R.F. 11.12.81				
Repetition	A/AA	90	73	70
	< 10	66	33	20
Reading	A/AA	90	83	73
	< 10	76	60	46
O.R.F. 14.12.81				
Repetition	A/AA	87	87	80
	< 10	73	70	50
Reading	A/AA	90	73	80
	< 10	80	77	60
R.A.N. 23.2.83				
Repetition	A/AA	93	80	86
	< 10	53	40	17

Results. The percentage correct score for each condition of these experiments for both patients are shown in Table 2. For O.R.F. on December 11, 1981 there was a strong effect of syllable length ($\chi^2 = 14.9$, 2 d.f., $P < 0.01$) and also of frequency ($\chi^2 = 26.5$, 1 d.f., $P < 0.01$) in repetition. Reading was significantly better than repetition (McNemar test $\chi^2 = 8.16$, $P < 0.01$). By December 14 there had been a significant improvement in O.R.F.'s ability to repeat single words (*see* Table 2): the syllable length effect had virtually disappeared and was confined to the low frequency three syllable words. The overall frequency effect remained statistically significant ($\chi^2 = 9.46$, 2 d.f., $P < 0.01$) but reading and repetition were now at virtually identical levels and there were no significant differences between them.

R.A.N. showed large effects of word frequency ($\chi^2 = 47.6$, $P < 0.01$) and an effect of syllable length ($\chi^2 = 6.1$, 2 d.f., $P < 0.05$). There was a high incidence of phonemic paraphasia both in O.R.F.'s and R.A.N.'s error responses. Phoneme substitutions were frequent as were reiterations, anticipations and deletions. Although a high proportion of both patients' errors were phonemic paraphasias there were also examples of word substitutions (lexical errors). R.A.N. made 9 such errors (13 per cent). For O.R.F. 66 errors were lexical of which the majority occurred in the reading condition (Sign test x = 6, $P = 0.007$).

Comment. This experiment has clearly established that word frequency and to a lesser extent word length are significant variables which affect O.R.F.'s and R.A.N.'s speech production. O.R.F.'s error rate on the repetition task was significantly higher than on reading in the first replication of this experiment, and considering both replications together there was a significant difference in the rate of his lexical errors in reading and in repetition tasks. The most common type of error shown by both patients in repetition tasks was a phonemic paraphasia which has been described as being typical of phonological disintegration in conduction aphasia (Dubois *et al.*, 1964).

Experiments 2a and 2b: Repetition and Recognition of Nonsense Syllables

In view of the clear and consistent effects of word frequency which were documented in the previous experiment it is of interest to examine the patients' ability to repeat and to recognize items which, in some sense, have a zero frequency in the language, namely, nonsense syllables. O.R.F. was tested on December 11, 1981. R.A.N. did not undertake this task.

Procedure. Experiment 2a. The stimuli which were employed for this phase of this experiment consisted of 41 words and nonwords from the material available in Glushko (1979). The material was selected so that nonword stimuli were meaningless both for auditory and for visual presentation, the words were the relevant phonologically matched controls from the same source. Word and nonword stimuli were presented in blocks according to an ABBA design.

Experiment 2b. Eighty nonword stimuli were generated for this experiment. All items were monosyllabic and comparable in structure to those employed in Experiment 2a (*see* Appendix 2). O.R.F. was required to decide whether a successively presented pair of stimuli were the same or different. Different pairs had a single phoneme discrepancy. All items were designed to be phonologically plausible according to the rules of English phonology. Half the trials required a same decision, and half a different decision. Items were presented by the experimenter who covered the lower half of her face to preclude the use of any visual cues for discrimination. As a control task the word phoneme discrimination task of Coughlan and Warrington (1978) was also presented.

Results. The results of these experiments are shown in Table 3. In Experiment 2a there was a highly significant word-nonword effect with words being superior to nonwords ($\chi^2 = 19.5$, $P < 0.001$). In Experiment 2b O.R.F. had very little difficulty with the successive recognition of nonwords, his overall level of performance comparing favourably with his score on the Coughlan and Warrington Word Discrimination task.

Comment. This study has shown that O.R.F. has a severe difficulty with the production of nonwords in a repetition task. However, he is able to make phonemic discriminations with successively presented nonwords. Following the logic of the Probe-Span task this finding indicates that his deficit with nonword repetition

TABLE 3. REPETITION AND RECOGNITION OF WORDS AND NONWORDS

Experiment 2a

Repetition of words and nonwords percentage correct

Words	*Nonwords*
85	39

Experiment 2b

Phoneme discrimination Words and Nonwords percentage correct

Words	*Nonwords*
100	95
n = 40	n = 80

cannot be attributed to a reduced capacity for holding verbal information in short-term storage, but rather, it points to impairment at the level of speech production. These findings extend the results of the previous experiment in which word frequency was shown to be an important variable insofar as there is an even greater deficit for nonwords as compared with real words for O.R.F.

Experiment 3: Sentence and Cliché Repetition

Clinical observation (T. Shallice and E. K. Warrington, unpublished data) has suggested that some patients with speech production deficits may have difficulty in a cliché repetition task. Therefore in view of the word length effect demonstrated in Experiment 1 it is of some interest to investigate O.R.F.'s and R.A.N.'s ability to repeat clichés and to contrast this with their repetition of novel sentences. A cliché, although composed of morphemes and usually obeying the syntactic rules of English, can be likened to a polymorphemic or polysyllabic word. Phrases such as 'put the cart before the horse' or 'turn over a new leaf' are tightly constrained in both their syntactic and lexical structure. With time the meaning of a cliché has become largely independent of the semantic referents of the individual lexical items. Thus they cannot be replaced by synonyms or varied in their order without changing the meaning of the whole phrase. It is generally accepted that in many cases a cliché has a single lexical entry although there are probably options for more flexible processing under certain conditions (Clark and Clark, 1977; Vihman, 1982).

Procedure. A set of 40 clichés was obtained from a dictionary of English Idiom (Wood and Hill, 1979); 40 short control sentences were generated that were of approximately the same length, phonological and lexical complexity as the clichés (*see* Appendix 3). O.R.F. was required to read and repeat both types of phrase. R.A.N. was only tested on the repetition task. The stimulus material was presented in 10 block trials of each phrase type according to a 4 × 4 Latin square design for O.R.F., and, for R.A.N., in an ABBA design. O.R.F. was tested on February 21, 1981, R.A.N. on February 23, 1983.

Results. A strict scoring criterion was adopted. Each phrase was only accepted as correct if all words were produced accurately and in their correct order. Self-

TABLE 4. REPETITION OF SENTENCES *VS* REPETITION OF CLICHÉS: PERCENTAGE CORRECT

	Sentence	*Cliché*
O.R.F.		
Repetition	85	50
Reading	60	63
R.A.N.		
Repetition	45	18

n = 40 item/cell

corrections were rare but allowed. The percentage correct for each condition of this experiment for both patients is shown in Table 4. For O.R.F. there were no significant differences between sentences and clichés in the reading condition. In the repetition condition both patients were significantly better at repeating a novel sentence than a familiar cliché (O.R.F.: $\chi^2 = 11.2$, $P < 0.01$; R.A.N.: $\chi^2 = 7.04$, $P < 0.05$).

Comment. The ability of both patients to repeat short sentences in this experiment was comparable to that obtained with their repetition of single polysyllabic words in Experiment 1. Indeed O.R.F. was more efficient at *repeating* sentences than reading them (presumably as a consequence of his dyslexia). This finding contrasts with O.R.F.'s performance with single words, where reading was reliably better than repetition. There were, however, no significant differences between the number of items correctly read in the sentence and cliché conditions in this experiment. Thus it is unlikely that the significant differences in the repetition conditions for either patient can be attributed to stimulus selection artefacts. If we assume that a cliché is similar to a polysyllabic word then the present results are entirely congruent with the evidence from the single word repetition task of Experiment 1, that is, O.R.F. and R.A.N. have particular difficulty with the articulation of low frequency polysyllabic words.

Experiment 4: The Effects of Sentence Context

One of the core characteristics of conduction aphasia is the severe impairment of speech production in a repetition task with the relative intactness of spontaneous speech. In spontaneous speech words are characteristically produced in a sentence context, whereas this is rarely the case in repetition. The aim of this experiment was to assess the effects of sentence context on O.R.F.'s ability to repeat individual polysyllabic words. It was not conducted with R.A.N.

Procedure (December 17, 1981). A set of 40 sentences was generated which had a critical terminal item which was a three-syllable low frequency word (*see* Appendix 4). O.R.F. was required (1) to repeat the terminal word from the sentence, and (2) to repeat the word presented in isolation. In addition he was required (3) to read the whole sentence and (4) to read the critical word in isolation. There were thus four conditions and the 4 (conditions) × 10 trial blocks were ordered in a Latin square design.

Results. O.R.F.'s responses were transcribed and only those which were phonemically accurate were accepted as correct. His performance was scored for only the critical item in each of the four conditions. His percentage correct score for each condition is given in Table 5. The overall effect of conditions was significant (Cochran $Q = 18$, $P < 0.01$). Further statistical tests revealed that this was due primarily to his relatively poor performance in the single word repetition task as compared to the single word reading task (McNemar $\chi^2 = 5.8$, $P < 0.02$) the effect of sentence context was not significant on the reading or recognition tasks.

TABLE 5. REPETITION AND READING OF TERMINAL ITEM IN A SENTENCE *VS* REPETITION AND READING OF SINGLE WORD PERCENTAGE CORRECT

Repetition		*Reading*	
Sentence	*Word*	*Sentence*	*Word*
50	40	63	65

n = 40

Comment. This experiment replicates the findings of Experiment 1 in that O.R.F.'s speech production is superior in a single word reading task than in a word repetition task. However, there were no significant effects of sentence context on word repetition in this experiment, although the demands of this task may not have maximized the contribution of contextual factors towards task performance.

Experiment 5: The Effect of Enforced Semantic Processing

In spontaneous speech words are not only produced in a sentence context, they are produced in a *meaningful* sentence context. The demands of Experiment 3 were possibly insufficient to ensure that O.R.F. attended to the meaning of the sentence. The present experiment was devized in order to maximize semantic processing of the context sentence.

Procedure 1. A further set of 20 sentences was generated, each having a critical three syllable low frequency item in their terminal position. A second set of 20 sentences was derived by substituting a single word (not the terminal item) which rendered the sentence 'nonsensible' (*see* Appendix 5). O.R.F. undertook this task on December 17, 1981, R.A.N. on February 23, 1983. O.R.F. and R.A.N. were required to repeat both the critical terminal item in the sentence context and the same word presented in isolation (as in the repetition conditions of Experiment 4). In addition they were asked to decide, in the sentence condition, whether an item made sense or was nonsense. The patients were asked to indicate their decisions nonverbally by nodding or shaking the head after repeating the terminal item. For O.R.F. sentence and word conditions were presented in blocks of 20 items according to an ABBA, BAAB, design; each item was therefore tested four times in each condition. For R.A.N., a single ABBA design was used; each item was therefore tested twice. In the sentence blocks 'sensible' and 'nonsensible' stimuli occurred equally often, and were pseudorandomized.

Procedure 2. This experiment was designed as a replication, using a larger pool of words and sentences. Forty additional low frequency three syllable words were placed in the terminal position of either a 'sensible' or 'nonsensible' sentence. The procedure was identical to that employed above except that stimuli were presented in 10 trial blocks and were tested twice in the sentence condition and twice in the single word condition for both patients. O.R.F. performed this task on December 21, 1981, R.A.N. on February 23, 1983. As the patients indicated their decisions about the 'sense' or 'nonsense' of the sentences nonverbally, there was insufficient nonambiguous data to analyse these decisions quantitatively. The qualitative impression was that this task was well within the capabilities of both O.R.F. and R.A.N.

Results. As in Experiment 3 the patients' responses were only accepted as correct if they were phonemically accurate. The percentage correct scores for each condition for both patients are shown in Table 6. In Procedure 1, O.R.F. was significantly better in the sentence condition (Wilcoxon $T = 9, P < 0.05$). R.A.N. showed a trend in the same direction which failed to reach significance (Sign test $x = 3$, $n = 12$, $P = 0.07$). In Procedure 2 the sentence condition was significantly better than the isolated word condition for both patients (O.R.F.: Sign test $x = 5$, $n = 20$, $P = 0.02$; R.A.N.: $x = 5$, $n = 20$, $P = 0.02$). There was no difference in performance between sensible and nonsensible sentence conditions in either procedure.

TABLE 6. EFFECTS OF ENFORCED SEMANTIC PROCESSING: REPETITION OF THE TERMINAL WORD IN A SENTENCE *VS* REPETITION OF A SINGLE WORD: PERCENTAGE CORRECT

	Sentence	*Word*	
Procedure 1			
O.R.F.	63	45	n = 80 trials
R.A.N.	65	50	n = 40 trials
Procedure 2			
O.R.F.	68	49	n = 80 trials
R.A.N.	66	50	n = 80 trials

Comment. This experiment has shown that when the patients' strategy options are constrained and they are forced to actively attend to the meaning of the stimulus, performance in a repetition task may be improved. This result was significant for O.R.F. on both Procedure 1 and Procedure 2 and for R.A.N. on Procedure 2. It is not possible to account for these findings in terms of 'task difficulty' since the dual task demands of imitation and performing a decision about a sentence would be, *a priori*, more complex than the single word repetition task. The results indicate that when a word *has* to be processed to the level of meaning, speech production is facilitated. When analysis at this level is not required, speech production in a repetition task is impaired.

In summary, the results of these experiments indicate that the speech production abilities of both patients with conduction aphasia are affected by task constraints. When a polysyllabic word, or idiomatic expression, is presented without a semantic context they have severe speech production problems. In contrast, when repetition of a word is contingent upon sentence processing, or processing for meaning, their level of performance is significantly better.

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Experiment 6: Single Word Repetition and Reading: Frequency and Syllable Length

Our aim in this experiment was to document A.R.T.'s speech production in a repetition task and to compare it with his speech production in reading aloud.

Procedure. This experiment was performed twice: first on September 19 and subsequently on October 22, 1982, when A.R.T.'s speech production had improved. The test stimuli consisted of one, two and three syllable low and high frequency words, a subset of those used in Experiment 1 (*see* Appendix 1). On the first of the two replications a subset of 24 words was presented and on the second a subset of 120. Reading and repetition were tested in an ABBA design.

Results. The frequency of correct responses on September 16 and the percent correct scores on October 22, 1982, are shown in Table 7. There was a significant difference between reading and repeating on both occasions (Sign tests: September 16: $x = 1$, $P < 0.001$, $n = 20$; October 22: $x = 9$, $P < 0.01$, $n = 30$). His reading aloud had improved by October 22, 1982 in parallel with the improvement of his spontaneous speech; however, A.R.T.'s ability to repeat single words remained significantly better than his ability to read them aloud. There were no effects of syllable length or frequency on either occasion.

TABLE 7. SINGLE WORD REPETITION AND SINGLE WORD READING

		Syllable length		
	Frequency	*1*	*2*	*3*
16.9.82				
Repetition	A/AA	4/4	4/4	3/4
	< 10	4/4	3/4	3/4
Reading	A/AA	2/4	0/4	0/4
	< 10	1/4	2/4	0/4
22.10.82 (% correct)				
Repetition	A/AA	85	90	90
	< 10	85	90	95
Reading	A/AA	80	70	65
	< 10	85	80	85

Comment. This experiment documents A.R.T.'s differential speech production abilities in reading aloud and repeating words, which were all well within the range of his comprehension vocabulary (in both presentation modalities). This pattern of results is the converse of that reported for O.R.F. (Experiment 1 *above*) who was significantly more impaired in repeating these words than in reading them aloud.

Experiment 7: Sentence and Cliché Repetition

This experiment was an exact replica of the repetition conditions of Experiment 3 (*see above*). Our aim in this experiment was to document A.R.T.'s ability to repeat novel sentences in contrast with his ability to repeat idiomatic phrases of English.

Procedure. Short sentences, which were either novel, or idiomatic English phrases (clichés), were spoken by the experimenter. A.R.T.'s task was to repeat them. The stimuli were presented in 10 trial blocks of clichés or sentences in an ABBA/BAAB design; 40 items of each type were tested (*see* Appendix 3).

Results. A.R.T.'s responses were strictly scored, only those items on which there were *no* speech production errors were accepted as correct. A.R.T. accurately repeated 73 per cent of the clichés, and 53 per cent of the sentences. This difference falls just short of significance ($\chi^2 = 3.4$, $P < 0.1$).

Comment. Although there was not a significant effect of stimulus type in this experiment there was a trend for clichés to be repeated more accurately than sentences. This is the opposite pattern to that observed in O.R.F. and R.A.N., who were significantly worse at repeating cliche's than repeating novel sentences.

Experiment 8: Effects of Enforced Semantic Processing

This experiment was almost an exact replica of Experiment 5 Procedure 2 (*see above*) which was devised in order to assess the effects of enforced semantic processing by O.R.F. and R.A.N.

Procedure. The materials were identical, namely, a set of 40 three syllable words which were presented in the terminal position of a sensible or nonsensible sentence context, or else in isolation (*see* Appendix 5). A.R.T. was required to repeat the critical word, following repetition in the sentence condition he was required to indicate whether the sentence he had heard was sensible or not by nodding or shaking his head. Words in isolation and words in context were tested in an ABBA/BAAB design on September 21 and a single ABBA design on October 22, 1982. The sense and nonsense context occurred equally often in the sentence condition, and the two types of stimuli were presented in a pseudorandom order.

Results. A strict scoring criterion was adopted. In order for responses to be accepted as correct, the critical word *alone* had to be articulated correctly. The percentage correct for both replications is shown in Table 8. There was a highly significant effect of sentence context. A.R.T. was significantly worse at repeating a single word presented in the context of a sentence than repeating a single word presented in isolation (Sign tests: September 21: $n = 38, x = 2, P < 0.01$; October 22: $n = 30, x = 2, P < 0.01$).

In the sentence condition A.R.T.'s errors were mostly intrusions of other items of the sentence string. This error type accounted for 62 per cent of his responses on the first occasion and 36 per cent on the second. Phonemic paraphasias were the next

TABLE 8. EFFECTS OF ENFORCED SEMANTIC PROCESSING: REPETITION OF TERMINAL WORD IN A SENTENCE *VS* REPETITION OF A SINGLE WORD: PERCENTAGE CORRECT

	Sentence	*Word*
21.9.82	27	87
22.10.82	45	93

most common error (30 per cent of his responses on September 21 and 15 per cent of his responses on October 22, 1982). Phonemic paraphasias only occurred occasionally with single word repetition (10 per cent and 3 per cent for the two replications).

Comment. A.R.T.'s performance was impaired by semantic context. This result is in direct contrast to that observed for O.R.F. and R.A.N., the patients with conduction aphasia. In terms of short-term memory capacity, O.R.F. and R.A.N. were at a distinct disadvantage, yet they were significantly aided by semantic context. A.R.T., with a superior short-term memory was hindered by semantic context, his competency in repeating single isolated polysyllabic words was far superior to that observed in O.R.F. and R.A.N.

Experiment 9: Sentence Repetition

The previous experiment has shown that A.R.T. was impaired when repeating the terminal item from a sentence processed for meaning. We wished to obtain further evidence that his deficit in repeating polysyllabic words in the terminal position of a sentence was independent of his somewhat reduced short-term memory capacity.

Procedure. The stimuli were those used in the sentence context condition of Experiment 8. A.R.T. was simply required to listen to the full sentence and to repeat it. The experiment was conducted twice, first on September 21 and again on October 22, 1982. The stimuli were presented in 10 trial blocks of their 'sensible' and 'nonsensible' forms; these blocks were ordered in an ABBA design.

Results. A.R.T.'s repetition performance was scored in two ways (1) on the full sentence, and (2) on the critical word occurring at the end of the sentence. A strict scoring criterion was adopted. In the sentence analysis the full string had to be produced without error; in the word analysis the critical item had to be accurately repeated. The percentage correct for both scoring procedures for both replications are shown in Table 9. A.R.T. was able to repeat the critical word accurately on the vast majority of presentations of the sensible sentences. On September 21 there was no significant effect of sentence type in either the sentence or the critical word analyses (Sign tests: $n = 24$, $x = 8$, $P < 0.08$ and $n = 14$, $x = 4$, $P = 0.09$, respectively). On October 22, 1982, sentence type had a significant effect on both his ability to repeat the single word and on his ability to repeat the sentence (Sign tests: $n = 13$, $x = 1$, $P = 0.002$ and $n = 15$, $x = 2$, $P = 0.004$, respectively). The minor trend for A.R.T. to repeat sensible sentences more efficiently than nonsensible sentences most probably reflects his sensitivity to the transitional probabilities

TABLE 9. SENTENCE REPETITION: PERCENTAGE CORRECT

	Sensible context		*Nonsensible context*	
	Final word	*Whole sentence*	*Final word*	*Whole sentence*
21.9.82	83	63	68	40
22.10.82	98	63	70	38

between words and to sentence structure, although other explanations could be considered.

As in the previous experiments there was a comparatively high incidence of phonemic paraphasic errors: these occurred in 38 per cent of A.R.T.'s total error responses. Nonneologistic errors occurred most frequently on function words, prepositions and adjectives and were also quite common on verb markers. Errors on nouns were very rare ('detector' → 'detective' was the only example). His errors were only infrequently paraphrases as has been reported in other aphasic syndromes (Saffran, 1982), but mostly an alternative meaningful sentence (e.g., 'in poor visibility never overtake' → 'in poor visibility nothing ever overtakes').

Comment. A.R.T.'s relatively efficient performance on sentence repetition contrasts with his impairment in Experiment 8 when he was simply required to repeat one word from a sentence which had been processed for meaning. The low incidence or errors on substantive words and the infrequency of paraphrases suggests that A.R.T. was not processing the material to the level of semantic analysis.

DISCUSSION

We have investigated the speech production deficits of three aphasic patients. O.R.F. and R.A.N., the two conduction aphasics, had relatively well preserved spontaneous speech but had great difficulty on single word repetition tasks, making a high proportion of phonemic paraphasic errors. Word length and word frequency effects were observed: their highest error rates occurred on low frequency polysyllabic words. A.R.T., a transcortical motor aphasic whose repetition of single polysyllabic words was very satisfactory, nevertheless had severely impaired spontaneous speech characterized by effortful initiation and a high proportion of phonological errors. We manipulated the semantic processing requirements of the repetition tasks: first by requiring the patients to attend to the sentence context in which the word was placed and secondly, by requiring them to repeat novel sentences and clichés. On those repetition tasks which we would argue were likely to maximize active semantic processing, the two conduction aphasics showed improvement; conversely the transcortical motor aphasic showed deterioration. The speech production deficits of both types of aphasia were therefore specific to particular conditions and were not the consequence of global disruption of speech output mechanisms.

Their speech production deficits did not appear to be a trivial consequence of impaired word perception, word comprehension or auditory short-term storage. First, both O.R.F. and R.A.N. were capable of performing phoneme discrimination tasks; indeed O.R.F.'s performance was at 'ceiling' level on both word and nonword tasks (Experiment 2). Secondly, both O.R.F. and A.R.T. scored at an excellent level on the Peabody Picture Vocabulary test indicating that their single word comprehension was intact, and R.A.N. was able to score within the average range which was considered to be close to his optimal level. Thirdly, our findings cannot be accounted for in terms of a short-term memory storage deficit. The two conduction aphasics did have an associated impairment in their auditory verbal short-term memory; however, their performance improved under conditions which made greater rather than lesser demands on short-term storage. Thus they were worse at repeating a single word in isolation than in the dual task conditions of the sentence context experiments. In addition the two conduction aphasics were more impaired on the cliché repetition task than on novel sentence repetition yet *a priori*, the memory load on the novel sentence task must be far greater than in the cliché repetition task. This is substantiated by the performance of A.R.T. He had a far superior auditory digit span but showed the opposite pattern to the conduction aphasics on sentence and cliché repetition tasks.

We have thus shown that the locus of the speech production deficits observed in these three cases does not arise in speech perception, comprehension or short-term storage. We would argue that the deficits lie in the transcoding of information *between* input and output systems. In both types of patient there was evidence of impaired speech production under specific conditions, and normal or near normal speech production under others. In both types of aphasia impaired speech was characterized by effortful laboured attempts to pronounce words which often resulted in phonemic paraphasic errors.

Perhaps the most striking finding of theoretical interest was that speech production deficits were specific to particular task demands. Spontaneous speech and word repetition in a sentence context favoured the conduction aphasics. Repeating individual words in isolation and repeating clichés favoured the transcortical motor aphasic. Following Lichtheim (1885) we would suggest that these double dissociations require the postulation of two separate processing routes for speech production. The speech production of the two conduction aphasics was significantly better in those tasks which maximized active semantic processing. The speech production of the transcortical motor aphasic was significantly better in those conditions in which processing for meaning was minimized. In information processing terms the conduction aphasic's speech production deficit can be conceptualized as damage to the phonological processing or transcoding route between speech perception and articulation. Analogously, the transcortical motor aphasic's deficits arise as a consequence of damage to the route between semantic analysis and speech production. This formulation is summarized in fig. 4.

We propose that there is an auditory/phonological transcoding process (D) between verbal input systems (A) and articulatory output systems (E) which bypasses verbal semantic systems (B). Damage to this processing route results in the syndrome of conduction aphasia, namely, impaired repetition with relatively well preserved spontaneous speech. This process is conceptualized as normally acting in a fast, automatic manner in word repetition tasks. Similarly there must be a second processing route for speech production from verbal comprehension (B) *via* semantic/phonological transcoding (C) to the articulatory output system (E).

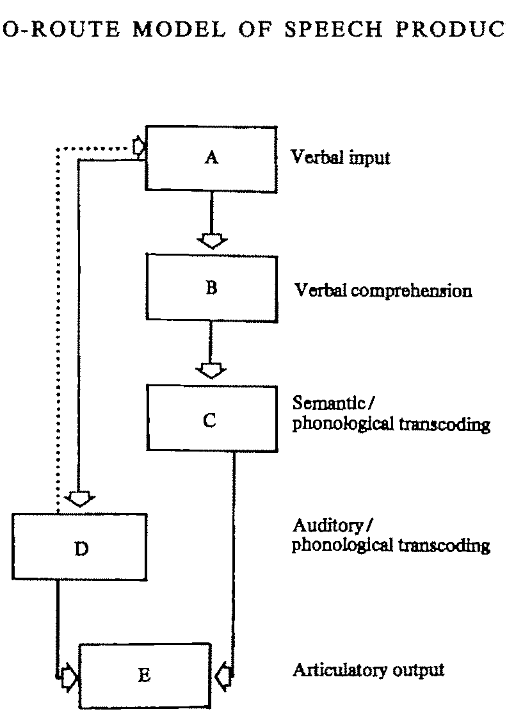

FIG. 4. A functional model of the speech production process.

Damage to this processing route results in the syndrome of transcortical motor aphasia, namely, of intact repetition but severe impairment of spontaneous speech. It is tentatively suggested that this system operates more slowly than system A–D–E in word repetition tasks and that its utilization is likely to require active control of processing in this context.

The present tentative model should be considered as a description of the double dissociations which we have obtained rather than as a literal or exhaustive account of the speech production process. The evidence indicates that there must be at least two independent routes involved in language production: one which is in some way dependent on active semantic analysis and another which is capable of passively transcoding auditory input for speech output systems (*see also* Morton, 1980). Although this model is very similar to the Lichtheim/Wernicke account, at this stage we would not wish to claim that our evidence necessarily indicates two disconnection syndromes. The quantitative evidence would be equally compatible with two separate processing deficits or indeed with a single processing deficit and a single disconnection. In the cases of conduction aphasia, the effects of word frequency, the partial accuracy of phonemic paraphasic responses, and the effects of word length and clichés in repetition tasks would perhaps be more compatible with an impaired phonological transcoding process than with a simple disconnection. The absence of word length and frequency effects and the striking discrepancy between excellent performance on difficult repetition tasks and total incapacity for propositional speech is perhaps most compatible with a disconnection syndrome in A.R.T. (although a processing deficit affecting speech initiation processes cannot be excluded). If our speculations are valid, O.R.F. and R.A.N. have an impaired auditory/phonological transcoding process, but for A.R.T. there may be a disconnection between word comprehension and semantic/phonological transcoding (*see* fig. 4). A more detailed error analysis than has been possible in the present study could perhaps clarify this issue.

Wernicke and Lichtheim suggested that the nonsemantic processing route was necessary as a feedback loop in error monitoring and word selection. We would speculate that perhaps it may be used as a means of refreshing or accessing material in an auditory input buffer and in this manner may thus be equivalent to part of the rehearsal loop which is intrinsic to many models of short-term retention (*see* Craik and Lockhart, 1972; Baddeley and Hitch, 1974). The full rehearsal loop would involve an additional processing route from D–A.

This account of speech production is formally very similar to current functional models of the acquired dyslexias and dysgraphias. Our data indicate that a two-route scheme for speech production deficits is also appropriate: however, as with our understanding of acquired dyslexia and dysgraphia, the biological necessity and *modus operandi* of dual processing routes in speech production remain obscure.

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APPENDICES

APPENDIX 1

Single Word Stimuli (Experiments 1 and 6)

brown
wrong
ground
chair
strike
child
room
song
view
true
sort
base
cause
watch
spring
life
much
wash
group
grass
plain
night
would
stream
fact
none
deep
vote
will
stood

almost
music
ready
nature
minute
include
country
college
teacher
question
practice
because
against
passage
weather
command
further
heaven
garden
master
finger
public
single
famous
beauty
island
party
never
refuse
silver

continue
discover
anything
exercise
suddenly
together
tomorrow
afternoon
different
president
newspaper
wonderful
department
understand
Washington
certainty
attention
character
government
deportment
important
article
general
various
national
direction
following
condition
industry
material

slap
prowl
noose
birch
tout
quirk
skimp
newt
trash
poach
etch
aisle
munch
gild
stew
twirl
feud
liar
brawl
mole
rinse
delve
limp
mute
coil
rook
wren
slang
flask
hark

prosper
rodent
stencil
sliver
robust
neutral
glimmer
notion
abstain
muslin
rocket
trample
slander
essay
muscle
denude
festoon
collide
typhoid
bracelet
lobster
slogan
lobby
hamper
wrestler
morass
flaxen
barter
poppy
quibble

skeleton
protector
notify
quotation
acrobat
mutiny
baroness
democracy
stimulant
revulsion
erratic
sinister
feverish
boundary
tyranny
porcupine
finery
lubricate
nicotine
gigantic
wilderness
sincerely
mosquito
ridicule
fixation
liaison
mutinous
cohesion
treachery
harmony

APPENDIX 2

Phoneme Discrimination Task. Different Stimuli (Experiment 2b)

doald	shoald	poave	puv
lale	zale	woan	woon
pillt	dillt	broave	bryve
koth	loth	sull	soll
drood	grood	suff	siff
pom	gom	ploave	ploab
lome	pome	steet	steen
dute	fute	keet	keeg
lool	mool	taze	tabe
pilld	dilld	moop	mool
boil	moil	belld	beffd
loal	lool	heef	heeg
grool	groal	tave	taze
beef	haff	moof	moob
dreed	droad	kose	kobe
nusst	nosst	pode	pone
poald	pilld	prine	prife
been	harn	ploar	ploase

APPENDIX 3

Sentences and Clichés (Experiments 3 and 7)

Take it with a pinch of salt
He's as deaf as a post
She got out of bed on the wrong side
He got my back up
Please give him a hand
Don't let the side down
It made my hair stand on end
Buy a pig in a poke
Bury one's head in the sand
Breathe down someone's neck

He's like a dying duck in a thunderstorm
It went in one ear and out the other
Down in the mouth
Get on the wrong side of him
Sight for sore eyes
Sign on the dotted line
I've something up my sleeve
Get something off your chest
He's had his chips
I'm down in the dumps

Put the cart before the horse
Every Tom Dick and Harry
Nothing to write home about
Keep body and soul together
Having your cake and eating it
Morning after the night before
Here today and gone tomorrow
Swallow it hook line and sinker
Put that in your pipe and smoke it
Six of one and half a dozen of the other

Thin end of the wedge
Under the weather
On top of the world
Turn over a new leaf
Take the rough with the smooth
Get off to a good start
Start off on the wrong foot
Too much of a good thing
Let the cat out of the bag
Take it with a pinch of salt

I like peanuts
He complains too much
He stayed for a week
I waited at the station for an hour
They travelled by boat
He was learning to type
The suitcase was too heavy to pick up
There are lots of fish in the river
It was a fine evening
He met me at the airport

The room was crowded
It was too hot
Everyone was in a hurry
He has lots of friends
They talked it over
She said she didn't mind
I enjoyed the play
He mended the plug
The pond was frozen
These dresses belong to me

It was too cold to go out
He finished his homework
The books were on the table
The apples were in the fruit bowl
She swept up the leaves in the garden
He finished drinking a cup of coffee
They went to school every day
We did the washing up in the kitchen
They went on holiday
I put the books away

The carpet is grey
He wanted to open the window
She went to buy some milk
It snowed all day
The radio was on
They went out to dinner
The clothes are in the wardrobe
I walked into the room
The newspapers are on the doorstep
The sweater is pink

APPENDIX 4

Sentence Context Stimuli (Experiment 4)

The girls danced in *formation*
To copy means to *imitate*
The fault was repaired by the *mechanic*
You can tell the date by looking at a *calendar*
We thought the price was *excessive*
The secretary sat at her *typewriter*
We must be on time for that *appointment*
Sherlock Holmes was a famous *detective*
This jacket isn't smart, it's *casual*
The rioters created a big *disturbance*

The baby is in the *nursery*
At Christmas giving presents is *customary*
She gladly accepted the *proposal*
The child screamed his *defiance*
His salary was barely *adequate*
This plant is a fine *specimen*
Membership of that club is quite *exclusive*
We bought the presents from a *catalogue*
I found his attitude *offensive*
The newsreader read the *bulletin*

This sale price is a good *reduction*
After the argument he left the room *abruptly*
Some people think that orchids are *exquisite*
His appearance is always *respectable*
Harry James is a news *reporter*
The Queen usually appears *dignified*
Christmas is a traditional *festival*
Stiff sentences were handed out by the *magistrate*
That clock is always *reliable*
The passing lorry set up a big *vibration*

The opposite of negative is *positive*
Dukes are members of the *nobility*
The professor was a Jewish *immigrant*
Canada and England are on the same *latitude*
The monster was *hideous*
With feeling he read the *quotation*
One can see the stars with a *telescope*
The snowdrift was a severe *obstacle*
The job depended on his *honesty*
The boxer was a worthy *opponent*

APPENDIX 5

nforced Semantic Processing: 'Sensible'/'Nonsensible' Sentences (Experiment 5, Procedure 1)

m taking lessons in car *maintenance*
m taking lessons in song *maintenance*

he hero was a great *patriot*
he hero was a wrong *patriot*

t breakfast I always eat *cereal*
t breakfast I always fly *cereal*

is blindness was a severe *handicap*
is blindness was a blue *handicap*

can't understand your *reasoning*
can't understand its *reasoning*

he heat was almost *tropical*
he heat was ready *tropical*

he workman was a *labourer*
he workman ran a *labourer*

He paid the attractive woman a *compliment*
He paid the attractive idea a *compliment*

The portrait was a *miniature*
The portrait saw a *miniature*

Tony Benn is a well known *socialist*
Tony Benn is a small known *socialist*

The newsreader read the *bulletin*
The newsreader sat the *bulletin*

A good typist is always *accurate*
A good typist is never *accurate*

Put rubbish in the bin to ensure its *disposal*
Put rubbish in the bin to look its *disposal*

An unmarried man is called a *bachelor*
An unmarried man is heard a *bachelor*

He studied the old *manuscript*
He studied the young *manuscript*

I could not see over the *partition*
I could not have over the *partition*

I will meet you at two o'clock *precisely*
I will meet you at two times *precisely*

I'm afraid I must give you a *refusal*
I'm afraid I must like you a *refusal*

Glass is usually *transparent*
Glass is never *transparent*

Those words were his final *utterance*
Those words were his yellow *utterance*

Experiment 5, Procedure 2; Experiment 8, Experiment 9)

he damage to his body was *internal*
he saucer to his body was *internal*

he scope was *limited*
he scope go *limited*

e couldn't find the book because of the *disorder*
e couldn't snow the book because of the *disorder*

he brilliant chemist invented a new *formula*
he brilliant chemist burnt a new *formula*

n elephant is *gigantic*
n elephant eats *gigantic*

e ate a lot because he had a large *appetite*
e ate a nothing because he had a large *appetite*

he argument was *circular*
he argument carry *circular*

he loving child was *affectionate*
he loving child sits *affectionate*

he book was valuable because it was a first *edition*
he book was valuable because it was a five *edition*

e used a ruler to make the *measurement*
e smiled a rule to make the *measurement*

he houses were built on a chosen *location*
he houses were sailed on a chosen *location*

uring the war the Germans planned an *invasion*
uring the war the Germans sang an *invasion*

he ornaments were used to *decorate*
he ornaments were hidden to *decorate*

he room is at the end of the *corridor*
he room is at the yellow of the *corridor*

The ascent of Everest was *perilous*
The ascent of Everest thinks *perilous*

The book created a *sensation*
The book rotated a *sensation*

The club has a large *membership*
The club has a few *membership*

In poor visibility never *overtake*
In poor visibility run *overtake*

After the wedding we went to a *reception*
After the wedding we caught to a *reception*

He repeated himself for *emphasis*
He swam himself for *emphasis*

I couldn't resist the *temptation*
I couldn't laugh the *temptation*

When something is upright it's *vertical*
When something is smelly it's *vertical*

The tree grew beside a *waterfall*
The tree grew after a *waterfall*

The sun rose on the *horizon*
The sun tapped on the *horizon*

The lie detector proved his *innocence*
The lie detector brushed his *innocence*

He wore glasses to help him see more *distinctly*
He wore dropped to help him see more *distinctly*

If you want to go I've no *objection*
If you want to go I've yes *objection*

To change means to *modify*
To change feels to *modify*

Einstein was a well-known *scientist*
Einstein was a well-flown *scientist*

We all had tea in the *pavilion*
We all had ring in the *pavilion*

The man who pulls rabbits out of a hat is a *magician*
The man who drowns rabbits out of a hat is a *magician*

The screaming child managed to *irritate*
The screaming child leaning to *irritate*

The future may be foretold by an *oracle*
The future may be foretold by up *oracle*

His politics were very *radical*
His politics were jelly *radical*

The match was won by a last minute *penalty*
The match was won by a last hour *penalty*

A minor is a *dependant*
A minor can a *dependant*

That tune has a pleasant *melody*
That tune has an orange *melody*

You should treat a church with *reverence*
You should jump a church with *reverence*

That cake was made by using a *recipe*
That cake was made by throwing a *recipe*

Athletes are often *muscular*
Athletes are never *muscular*

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ON-OFF FLUCTUATIONS IN PARKINSON'S DISEASE

A CLINICAL AND NEUROPHARMACOLOGICAL STUDY[1]

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SUMMARY

On-off fluctuations have been studied in twenty patients with Parkinson's disease on long-term levodopa treatment. The pattern of fluctuations was related to the timing of oral levodopa ingestion in all patients. 'Predictable' fluctuators were characterized by fewer daily doses taken at longer intervals than 'unpredictable' fluctuators in whom individual dose responses tended to overlap. Most patients at least once a day experienced an unexplained failure of an oral dose to take effect.

Administration of levodopa by intravenous infusion at a constant rate brought about a dramatic extension in the duration of mobility and reduced the frequency of fluctuations compared with oral therapy; apomorphine consistently reversed off phases when administered shortly after their onset, whereas lisuride was less often effective.

We conclude that the development of a sustained-release formulation of levodopa would lead to improved control of the response fluctuations seen with conventional levodopa preparations.

INTRODUCTION

Prior to 1967 Parkinson's disease was generally regarded as a chronic condition which slowly and steadily deteriorated. Apart from the uncommon and bizarre manifestations of 'kinesia paradoxa' seen in the aftermath of von Economo's encephalitis, the only striking diurnal fluctuations in patients' disability that were acknowledged comprised emotionally-induced variations in tremor (Marsden and Owen, 1967), and motivational changes in bradykinesia including the phenomenon of 'freezing' (Schwab *et al.*, 1959).

Since the introduction of levodopa-containing preparations for the treatment of Parkinson's disease, initial reports of therapeutic benefit (Birkmayer and Hornykiewicz, 1961; Cotzias *et al.*, 1967, 1969) have been so widely confirmed that some would regard the response to levodopa as a diagnostic criterion. Unfortunately, after several years of treatment almost all patients gradually deteriorate, regarded as progression of the underlying disease process, but in addition some show prominent variations from hour to hour in their symptoms and signs.

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[1] Preliminary results of this study were given at the Seventh International Symposium on Parkinson's Disease, at Frankfurt, June 1982.

Reprint requests to Dr G. M. Stern.

TABLE 1. FLUCTUATIONS IN MOTOR PERFORMANCE COMMONLY SEEN IN PATIENTS WITH PARKINSON'S DISEASE ON CHRONIC LEVODOPA THERAPY

Hyperkinetic	Peak-dose chorea Diphasic dyskinesia
Dystonic	Early-morning dystonia End-of-dose dystonia Peak-dose dystonia
Hypokinetic	Akinetic 'freezing' of gait Early-morning akinesia End-of-dose deterioration, 'wearing-off effect' Sudden 'switching off'

The commonly recognized patterns of disordered movement seen on chronic levodopa therapy are set out in Table 1. With the possible exception of akinetic freezing, all these phenomena appear to be related to the timing of oral levodopa. Phrases such as 'peak-dose' and 'end-of-dose' are self-explanatory; early morning dystonia (Lees *et al.*, 1977*b*) and early morning akinesia occur on waking, after the night long drug-free interval.

The most frequent short-term fluctuation in motor performance takes the form of a 'wearing-off' effect, or 'end-of-dose deterioration', which occurs in about two-thirds of patients treated with levodopa for six years (Shaw *et al.*, 1980). Yet many investigators have failed to find a consistent correlation between plasma levodopa concentration following a single oral load and either the magnitude or the timing of the clinical motor response (Muenter and Tyce, 1971; Hinterberger and Andrews, 1972; Rinne *et al.*, 1973; Bergmann *et al.*, 1974; Pilling *et al.*, 1975; Algeri *et al.*, 1976; Galea-Debono *et al.*, 1977; Rossor *et al.*, 1980). There are many difficulties in interpreting the results of such levodopa 'tolerance tests'. These difficulties include age, body weight and drug history of the patients studied; inclusion of wrongly diagnosed patients; whether the patients were fasting or not; the effects of coadministration of a decarboxylase inhibitor; the frequency of blood sampling; and the sensitivity of scoring systems and biochemical assays. All studies, however, are unanimous in stressing the extreme intersubject variability in levodopa handling (Wade *et al.*, 1974). In some cases, plasma concentrations have been correlated with the presence and severity of (peak-dose) dyskinesia but not with clinical improvement (Reid *et al.*, 1972; Rinne *et al.*, 1973), although it has been appreciated that absence of a clear and direct correlation between plasma level and biological response would be expected for a drug which requires metabolic activation.

Much less commonly than a 'wearing-off' effect, abrupt and spectacular transformations may occur. A patient may be shuffling, bowed and drooling in an apparently advanced stage of parkinsonism, yet, literally within minutes, he may be striding boldly and indistinguishable from normal. Many victims have likened the apparent metamorphosis to the operation of an imaginary switch inside the nervous system, and the terms 'on-off' fluctuations and even 'on-off syndrome' have gained acceptance by common usage.

Although precise definition of these clinical states remains controversial, we include only those patients who exhibit abrupt and extreme alterations in motor performance occurring over the course of a few minutes several times daily. After six years of levodopa treatment about 10 per cent of patients with Parkinson's disease come within this definition (Shaw *et al.*, 1980). Amongst such patients there is doubt as to whether the timing of the on-off phenomena is clearly related to the ingestion of oral levodopa, that is, a more exaggerated form of the wearing-off effect and therefore 'predictable'; or whether the changes are totally unrelated to drug administration and thus 'unpredictable'. Attempts to correlate these more sudden and severe on-off fluctuations with plasma levodopa levels have yielded equally conflicting results, although when studied over the course of a whole day at least some patients show a consistent relationship (Fahn, 1974; Sweet and McDowell, 1974; Tolosa *et al.*, 1975; Papavasiliou *et al.*, 1979). Tolosa *et al.* (1973) reported that increasing the size and frequency of dosage abolished the clinical fluctuations, but this was neither practicable in many patients because of the emergence of dose-limiting adverse reactions nor could this success be confirmed by others. Shoulson *et al.* (1975) found that an intravenous infusion of levodopa given at a constant rate for four hours was sufficient to sustain mobility in 5 patients, but because these patients remained fasted and supine throughout the experimental period conclusions upon motor response were limited. Similar improvement was also reported by Quinn *et al.* (1982) in 3 patients during continuous, but not constant rate, infusion in an uncontrolled trial.

Interpretation is further complicated because the abrupt 'switching on' and 'switching off' do not always occur in fixed temporal relation to oral ingestion of levodopa. Many patients insist that their daily cycles of mobility occur at random through the day. Studies of clinical state and simultaneous plasma levodopa measurements have added to the apparent confusion by identifying mobile subjects with negligible plasma concentrations and immobile subjects with very high levels. Indeed some patients seem to switch on and off so rapidly and frequently that the term 'yo-yo-ing' has been advocated (Marsden and Parkes, 1976), implying total independence from timing of levodopa ingestion and absorption. However, the same authors (Quinn *et al.*, 1982) have also reported that careful observation may disclose a correlation between timing of dose and apparently dose-unrelated, random fluctuations.

Accordingly, numerous speculations and hypotheses have been advanced to explain on-off fluctuations independent of plasma levodopa concentrations and of subsequent dopamine formation in the basal ganglia, the presumed mechanism of action of the amino acid. Intrinsic neuronal rhythms of endogenous catecholamines (Barbeau, 1972) or their catabolic enzymes (Birkmayer *et al.*, 1975) have been invoked; the formation of tetrahydroisoquinolines, alkaloid condensation products of dopamine, might mediate (Sourkes, 1971) or antagonize some of the therapeutic actions of levodopa (Sandler, 1974); denervation hypersensitivity (Ungerstedt *et al.*, 1971; Lee *et al.*, 1978) could account for the progressive rise in the prevalence of levodopa-induced dyskinesia, although other suggestions implicate 3-O-methyl-dopa (Ericsson, 1971; Feuerstein *et al.*, 1977) or excessive noradrenaline formation (Birket-Smith and Andersen, 1973). Fahn (1974) concluded that sudden desensitization of striatal dopamine receptors, perhaps caused by a phenomenon analogous to depolarization block at the neuromuscular junction following excessive stimulation, could account for the on-off phenomenon.

In an attempt to elucidate the role of pharmacokinetic and pharmacodynamic mechanisms, we have studied in three ways a group of patients with on-off fluctuations in motor response to levodopa: (1) observations of the patterns of fluctuations in relation to the timing of oral levodopa preparations; (2) double-blind crossover comparison of oral levodopa with constant rate intravenous administration in ambulant patients; (3) examination of the responsiveness of patients to the dopamine receptor agonists lisuride and apomorphine administered parenterally shortly after the onset of an akinetic phase.

PATIENTS AND METHODS

Twenty patients (8 female, 12 male) with idiopathic Parkinson's disease aged between 42 and 68 years (mean 55 years) were studied while inpatients for two to four weeks. Patients were selected because each had severe incapacitating on-off fluctuations in their motor response to levodopa and showed no evidence of intellectual impairment. All patients volunteered to participate after the purposes, risks and potential benefits of each part of the study had been explained to them in the presence of a close relative. The investigation protocols had been approved by the Ethics Committee of University College Hospital. The clinical details of each patient are summarized in Table 2. Apart from 5 patients (Cases 8–12) on anticholinergic therapy, no other drugs were taken.

An illustrative example is Case 10. In 1970 at the age of 45 years he developed right-sided hemiparkinsonism and took levodopa, initially with good effect. Intermittent response obliged his retirement in 1974. Abrupt changes in mobility have become gradually more conspicuous. Walking and handwriting are essentially normal at times, but during off periods he is unable to write and requires help to rise from a chair and to walk.

Throughout the study, patients ate usual hospital meals at 0730, 1200 and 1800 h daily, and were fully clothed and ambulant. They were encouraged to be as active and independent as possible in the ward in order to simulate their usual level of daily activity.

Initial Assessment, Observations and Documentation of Patterns of Fluctuations

All 20 patients continued their usual optimal outpatient drug regimes. Each took his own doses of the appropriate combined preparation of levodopa with a peripheral decarboxylase inhibitor at intervals, either fixed or variable according to individual custom. They were trained in the use of self-scoring diaries (Lees *et al.*, 1977*a*) in which they recorded the time of ingestion of each dose of levodopa and the times at which the sudden 'switching on' and 'switching off' occurred. These diaries were supervised throughout each day for a minimum period of five days and augmented by continual clinical assessment by one of us (R.J.H.) based upon the Webster Disability Rating Scale (Webster, 1968).

Comparison Between Oral Levodopa and Intravenous Infusion

In order to carry out a valid comparison, the peripheral decarboxylase inhibitors (PDI) benserazide or carbidopa were administered separately at fixed intervals for the duration of the trial. The daily dose corresponded as closely as possible to the normal intake of each patient. On days 1 to 2, 100 mg levodopa capsules were substituted for the combined levodopa-PDI preparation and the patients assessed further. To avoid the potential hazards of provoking thrombophlebitis by infusing large volumes of an acidic solution (pH about 3) we elected to administer the infusion *via* a central venous cannula direct into a subclavian vein. This had the additional advantage of allowing complete freedom of movement for both arms since no external splint was necessary. Percutaneous subclavian cannulation was carried out under local anaesthesia on day 3. A solution of 200 mg levodopa (5 mg ml^{-1}) was added to 250 ml Normal saline infusion containers giving a final concentration of 0.69 mg ml^{-1}.

Determination of dose response. The infusion, regulated by an automated drip controller, was started on day 3 at a rate estimated from each patient's daily levodopa requirement and increased every 2 h until a satisfactory and sustained response was achieved. This administration rate was used unchanged for the remainder of the trial.

Double-blind comparison. On days 4 to 7 the effects of oral and intravenous levodopa were compared in a crossover study. On two days the patient took active levodopa capsules orally whilst receiving a Normal saline infusion as control. On the other two days, identical placebo capsules were taken during levodopa infusion. The infusions, active or placebo, were administered for at least 7 h, and in most cases 12 to 16 h/day. Overnight Normal saline was infused slowly to keep the cannula patent. Patients continued to maintain self-scoring diaries and an independent observer assessed clinically each subject at quarter hourly intervals throughout the day. Because of painful early morning dystonia, 5 patients (Cases 1, 3, 4, 17, 18) required an active 'booster' dose of levodopa at 0500 to 0600 h every morning of the trial; this was given in an open manner, but all the remaining doses were double-blind. On two consecutive days, blood samples were taken for estimation of plasma concentrations of levodopa and 3-O-methyldopa. Details of the protocol and analytical method will be published elsewhere.

Acute Drug Challenges During Off Periods

Over the course of a two to five day period whilst taking their usual outpatient medications, 13 patients received several injections of lisuride and/or apomorphine 10 to 15 min after the onset of a spontaneous off period. The effects were assessed both by clinical examination and by means of a pegboard test of motor performance. The trial design was double-blind, and parenteral injections of Normal saline were given as controls.

Lisuride at a dosage of 75 to 150 μg according to body weight was given intravenously, dissolved in Normal saline, to patients pretreated with 20 mg domperidone four times/day. Nonresponders were subsequently given a higher dose of lisuride, side effects permitting. Apomorphine (1 mg) was given subcutaneously without domperidone pretreatment.

Statistical Methods

The mean levodopa dosage interval, together with mean response latency (time to take effect) and duration of clinical response for each effective oral dose, were calculated for the whole five-day assessment period. For the infusion study, the response was defined as the total time spent 'on' during the daily experimental infusion period expressed as a percentage of the duration of that infusion period. The percentage improvement was calculated for each pair of crossover days.

The mean number of daily on-off cycles was also calculated for the four days of oral treatment (including the initial assessment days 1 and 2), and for the two full infusion days, and the differences compared for each patient. Levels of significance were determined by a two-tailed Wilcoxon Signed Rank test applied to each pair of values. Nonparametric confidence limits were calculated for the sample median change in both variables.

TABLE 2A. PATIENTS WHO BELIEVED THEIR RESPONSE FLUCTUATIONS TO BE UNPREDICTABLE

			Duration (yrs) of			*Hoehn and Yahr (1967)*							
Case	*Sex*	*Age (yrs)*	*Disease*	*Dopa therapy*	*On-off*	*Min*	*Max*	*Daily levodopa dosage (mg)*	*Daily doses*	*Mean dosage interval (h)*	*Mean response latency (min)*	*Mean duration of response (min)*	*Peak-dose chorea*	*End-of-dose dystonia*
1 (V.B.)	F	46	11	10	7	4	5	1100	11	1.5	52	71	++	+
2 (D.C.)	F	59	18	12	8	4	5	700	7	2.0	39	98	+++	0
3 (S.C.)	F	52	15	4	2	2	2	1000	5	3.0	60	151	+	+
4 (L.D.)	M	56	17	11	8	2	4	1250	10	1.5	47	82	++	+
5 (R.F.)	M	53	14	12	5	2	4	400	4	4.0	44	96	+	0
6 (P.J.)	M	59	14	9	6	3	5	1000	5	2.5	74	82	+++	0
7 (V.J.)	F	56	11	11	5	4	5	700	7	2.0	68	64	+++	+
8 (B.M.)	F	60	9	9	8	2	3	500	10	1.5	35	84	++	+
9 (N.M.)	M	42	10	8	4	2	5	650	5	3.0	51	125	++	+
10 (R.O.)	M	57	12	12	5	2	5	800	8	2.0	96	130	++	+
11 (A.S.)	M	61	7	7	6	2	5	1500	12	2.0	43	73	++	+
12 (D.W.)	M	62	19	11	8	4	5	800	7	2.0	47	84	+	0

TABLE 2B. PATIENTS WHO BELIEVED THEIR RESPONSE FLUCTUATIONS TO BE PREDICTABLE

			Duration (yrs) of			*Hoehn and Yahr (1967)*							
Case	*Sex*	*Age (yrs)*	*Disease*	*Dopa therapy*	*On-off*	*Min*	*Max*	*Daily levodopa dosage (mg)*	*Daily doses*	*Mean dosage interval (h)*	*Mean response latency (min)*	*Mean duration of response (min)*	*Peak-dose chorea*	*End-of-dose dystonia*
13 (D.B.)	M	51	8	8	3	2	5	1500	6	3.0	44	158	+	+
14 (B.C.)	F	63	12	11	3	2	2	700	7	3.0	45	146	+	0
15 (M.J.)	M	55	10	9	2	2	3	1000	4	4.0	51	108	+	0
16 (I.M.)	F	58	10	8	4	2	3	750	3	5.0	45	243	++	+
17 (R.M.)	M	59	10	8	3	2	3	1000	4	3.5	77	145	++	+
18 (I.R.)	M	66	11	9	5	2	3	700	7	2.5	67	103	+	+
19 (P.R.)	F	68	7	6	3	2	2	300	3	4.0	76	157	+	0
20 (G.T.)	M	54	13	10	7	2	5	1000	5	3.0	63	110	+	0

RESULTS

Pattern of Spontaneous Fluctuations on Oral Levodopa Therapy

Prior to assessment all 20 patients considered their fluctuations to be unpredictable. Twelve believed their patterns to be totally random, a view consistently shared by their spouses; their clinical details are given in Table 2A. The remaining 8 described an essentially predictable pattern of cyclical response to each oral dose, interrupted by occasional and inexplicable failure of individual doses to have any discernible effect (Table 2B).

Severity of fluctuations. All patients were at least stage 2 on the Hoehn and Yahr disability rating scale (Hoehn and Yahr, 1967). Three remained stage 2 despite abrupt and conspicuous fluctuations which in these patients mostly involved tremor and peak-dose chorea in the nondominant limbs. All the others fluctuated by at least one stage of functional disability: 9 by one stage; 3 by two stages; and 5 patients regularly switched from stage 2 (totally independent) to stage 5 (confined to bed or chair) and back each day.

Pattern of fluctuations. A clear cyclical response to levodopa was easily discernible in the patients listed in Table 2B. On average, however, at least one daily dose failed to give clinical benefit. Observation revealed an identical dependence of the fluctuations of patients in Table 2A, obscured because the mean dosage interval was shorter (2.0 *vs* 3.6 h) in this group, hence giving an overlap effect. Based on this assumption a mean duration of action has been calculated for both groups.

Four patients (Cases 3, 15–17) experienced significant sleep benefit, so that their disability was only minimal on waking but increased gradually over the next hour. The remainder were profoundly disabled on waking (early-morning akinesia) and were obliged to take their first daily dose immediately.

In 3 patients (Cases 8, 10, 13) after a large meal at 1200 h, the postprandial dose of levodopa consistently failed to produce benefit.

Dystonic phenomena. Two patients showed peak-dose dystonia. Case 8 had continuous dystonic flexion of one knee with inversion of the foot during all periods of mobility; Case 9 experienced occasional but extremely painful tonic-clonic torticollis at times of excessive peak-dose chorea.

Dystonic foot postures occurred daily in 7 patients on waking. In 2 the condition was self-limiting lasting less than half an hour, but in the others was reversed only by levodopa (or an injection of lisuride in 3 cases). One of the latter, Case 4, regularly experienced a more complex dystonic involvement of the whole lower limb. Other dystonic phenomena related to end-of-dose periods are listed in Table 3. The term 'cramp', invariably used by all these patients, describes the association of pain and stiffness with visible or palpable muscle spasm. These phenomena appeared to be constant sequelae of drug withdrawal. The following history illustrates the consequences of withholding levodopa.

TABLE 3. END-OF-DOSE DYSTONIC PHENOMENA

Case No.	
1	Shoulder abduction to 90 deg, hyperflexion of elbow and wrist, hyperextension of digits.
3	Backache and bilateral toe curling.
4	Hyperflexion of hip, knee and ankle and four toes with extension of the hallux.
7	Severe backache.
9	Foot inversion, toe curling.
11	Bilateral foot inversion and toe curling.
13	Painful neck cramp and occasional complex retro- and torticollis.
14	Painful bilateral shoulder cramp.
16	Foot inversion, toe curling and unilateral forearm cramp.
17	Bilateral toe curling, unilateral foot inversion.
18	Bilateral foot inversion and toe curling.

Having had her last 100 mg levodopa at 2300 h the previous night, Case 1 woke at 0700 h and within minutes the right shoulder became fixed in 90 deg of abduction, the elbow and wrist both hyperflexed with fingers hyperextended and splayed—her usual morning 'cramp', which normally passed off 30 to 45 min after the first 100 mg dose of the day. Over the next 2 h she remained profoundly immobile while fixed in this grotesque dystonic posture which could not be overcome passively and which became progressively more intense and painful. Cogwheel rigidity was mild in the left arm and marked in both legs. She was just able to stand unsupported but unable to take a single step. By 0930 h her head had become tonically rotated towards the elevated right arm with superimposed clonic flexion and extension occurring about every minute, and she became more and more furiously agitated. There was a sinus tachycardia of 120/min with profuse sweating and a normal blood pressure; the facial muscles were contorted in pouting, grimacing, nose twitching and blinking successively or all at once, with jaws clenched, making it impossible to remove her dentures; her left arm became clamped in an adducted 'hemiplegic' posture with insuperable rigidity at all joints; her voice was almost inaudible and she was sometimes incapable of speaking for several minutes. By 1200 h she was nauseated and drooling profusely, unable to swallow, with rapid irregular respirations and stridor, painful sustained retrocollis and total anarthria. Both lower limbs were forcibly flexed at the hips and knees, with inversion of the feet and curling of the toes. A slow intravenous infusion of levodopa (20 mg h^{-1}) was started at 1245 h and within an hour the storm gradually passed. The dystonic postures cleared and she was left, exhausted and profoundly akinetic, sitting motionless on the edge of her bed. She was able to talk softly, drink with a straw and touch each finger with the thumb in the left hand while the right hand remained immobile. She could stand unsupported but not take any steps. As she remarked herself, 'it's all quiet now'.

Similar though less dramatic experience with another patient, Case 4, led us to include an early morning active 'booster' dose of 100 mg oral levodopa in the infusion protocol for such patients.

Choreiform dyskinesia. All 20 patients had conspicuous dyskinesia sufficient to impair normal activities throughout each on period. None was detectable before the first daily dose of levodopa. The severity, consistently increased during the performance of synkinetic movements, was greater in the 'unpredictable' group because of the overlap effect of consecutive doses (*see* Table 2). Although the term peak-dose chorea is often used, dyskinesia did not gradually build up and subsequently decline but was simply either present or absent, its severity influenced by mental concentration and synkinetic activity. Its distribution was usually generalized, affecting proximal and distal limb musculature and the neck more than the trunk and orofaciolingual muscles.

Switching on and switching off. Two patients clearly showed diphasic dyskinesia, that is, florid involuntary movements coinciding with onset and cessation of the levodopa effect on akinesia and subsiding in between. Case 4 experienced rapid violent alternate kicking movements of the legs, lasting 4 to 5 min on each occasion. Case 9 developed alternating pronation and supination of the right wrist associated with lightning rippling movements of the fingers of both hands for a similar duration. Both had more generalized dyskinesia during the remainder of each on period.

Observation revealed that a further 14 patients had a stereotyped pattern of involuntary movements as the prelude to switching on but not to switching off. Most patients were aware of their premonitory significance. The stereotypes included choreiform flexion and extension of one or both knees; a more compound 'stirring' motion with one leg; abduction and adduction of a hip; flexion and inversion of a foot followed by placing the fingers of one hand against the face with hyperpronation of the wrist and abduction of the shoulder; and in one case repetitive beard stroking. Some of the more compound stereotypes became incorporated into complex mannerisms which patients rationalized as having a purpose such as 'stretching' or 'yawning', or into organized rituals devised to help to bring themselves 'on'.

The transformations of switching on and off were complete within five, or rarely ten, minutes. Involuntary movements usually began before any improvement in motor performance was demonstrable, and in some cases a number of abortive flurries of dyskinesia occurred at decreasing intervals beforehand. Rather than a gradual steady improvement, akinesia seemed to lift virtually instantaneously, so that whilst completing a pegboard test the patient appeared to 'change gear' and accelerate rapidly. Thereafter, motor performance remained fairly constant. Often the first hint of being about to switch off was the sudden reappearance of tremor during relaxation, which was abolished by synkinetic movement and exchanged for dyskinesia. Sometimes a period of alternating tremor and dyskinesia could last for ten minutes before the decline in motor performance, which invariably became complete within one or two minutes. Akinesia was usually most profound immediately after this switching off, and there was a tendency for slight improvement over the succeeding hours. Motor performance was particularly susceptible to the variable influences of emotion, stress and motivation at this time. Not infrequently, hesitancy and 'freezing' of gait appeared some minutes before, and independent of, impairment in manual dexterity. Hypotonia was often present in the early stages of an off period, but was gradually replaced with parkinsonian rigidity later.

Fluctuations in mood. We were struck by alterations in mood which accompanied on-off fluctuations. Although it was difficult to quantify such frequent alterations using conventional psychiatric symptom rating scales, only two patients (Cases 18, 19) denied bouts of depression. Eighteen patients described significant depressive symptoms during off periods.

In 2 patients cyclical swings in mood, which occurred *pari passu* with the fluctuations in motor performance, were severe. Case 3 had a sad, despairing mood, accompanied by delusions of guilt and unworthiness, but only during off periods; her affect was entirely normal at other times. This patient's emotional retardation was more disabling than her parkinsonism. Case 13 was literally hypomanic-depressive several times each day and became withdrawn, depressed and obsessed

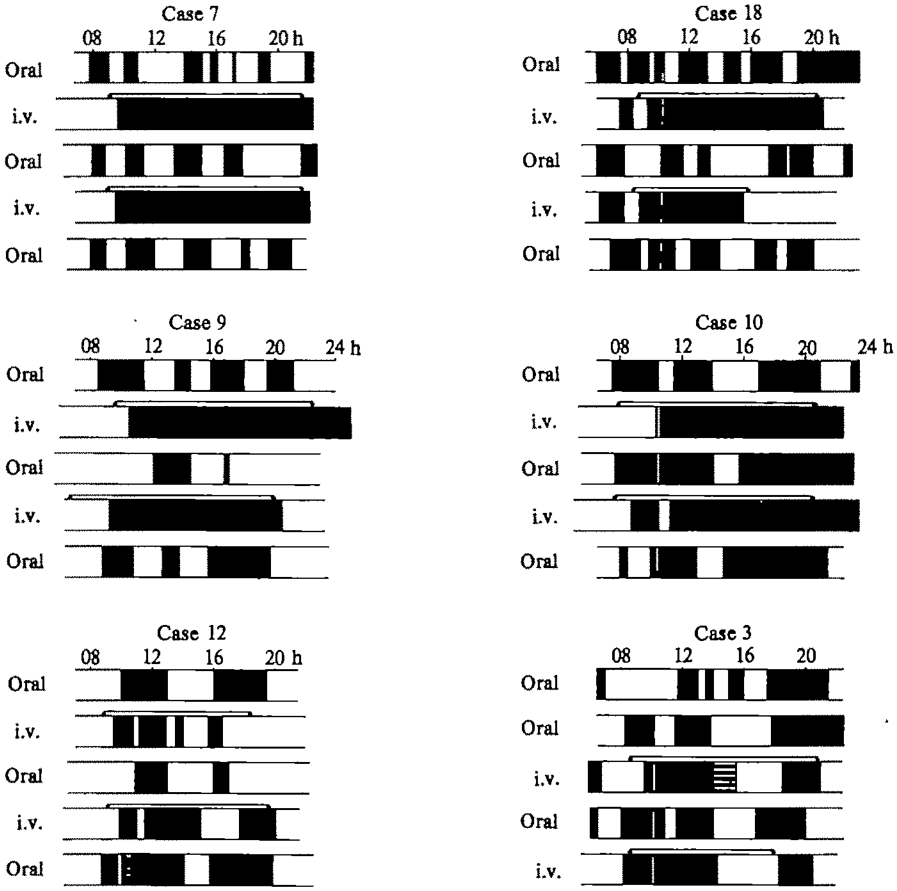

FIG. 1. Daily on-off charts in 6 patients. Each pair of horizontal lines indicates the extent of a waking day. Black bars denote on periods; off periods are open. Coexistent features of on and off states are shown by horizontal stripes. The top day shows a representative day during the initial assessment period. The remaining four days show the results of the four-day crossover comparison of oral and intravenous levodopa. The duration of the active infusion is shown by the bar above each intravenous day.

with hypochondriacal notions and paranoid delusions during off periods. Yet almost immediately he could become euphoric and irritable, with pressure of speech, physical hyperactivity and grandiose charitable ideas which have led him to the fringes of bankruptcy several times.

Response to Intravenous Levodopa Infusion

Because of the unequivocal nature of his condition, it was always possible for both the patient and the 'blind' observer to agree simply whether the patient was on or off. The quality of the response and the manner of the transition were identical on oral and intravenous therapy. Two patients (Cases 3 and 17) showed a curious transient coexistence of generalized or unilateral chorea with generalized or contralateral tremor, which had not been seen previously in either patient. Fig. 1 gives diagrammatic representations of the results from 6 patients.

Twelve of the 14 patients studied showed a definite and marked response to intravenous infusion of levodopa at rates of 32 to 80 mg h^{-1} (fig. 1, Cases 7, 9, 10, 18). Two non-responders failed to show a net increase in the duration of on periods during levodopa infusion at the rates employed (fig. 1, Cases 3 and 12). For technical reasons the data of 2 of the responders were incomplete, and the results from 12 patients are presented numerically in Table 4. For the whole group of 12 patients the median response was 90 per cent during levodopa infusion, with a median improvement in response compared with oral therapy of 25 per cent ($P < 0.01$). There was a median reduction in the number of daily on-off cycles of 1.9 ($P < 0.01$). The nominal 95 per cent confidence limits for these median values are shown in Table 4.

Two patients, Cases 4 and 15, received levodopa infusions on two consecutive days, days 5 and 6, and oral therapy on days 4 and 7. In both instances the response was sustained only on the first infusion day, when they were both on for 92 per cent of the infusion period. Despite identical drug administration rates their responses were 44 and 64 per cent, respectively, on the second. A third patient, Case 7, in

TABLE 4. RESULTS OF INTRAVENOUS LEVODOPA INFUSION

	Oral levodopa			*Intravenous levodopa*				
Case No.	*Hours on/day*	*Response (%)*	*Cycles/day*	*Infusion rate/mg h^{-1}*	*Infusion period/h*	*Response (%)*	*Cycles/day*	*Increase in response*
3	8.2	65, 61	3.7	60	12.1, 9.1	56, 61	2.5*	−9, 0
4	8.1	52, 49	4.0	48	14.4, 15.7	92, 44	3.5*	40, −5
7	6.2	42, 47	5.7	54	12.5, 12.6	95, 96	1.0	43, 39
9	7.6	48, 49	3.3	52	12.8, 13.3	94, 81	1.0	46, 32
10	11.4	86, 73	3.0	37	12.6, 12.8	87, 86	1.5	1, 13
12	6.3	33, 78	2.7	60	9.5, 10.5	47, 63	3.5	14, −15
14	8.1	64, 51	3.7	38	7.8, 11	89, 92	1.0	25, 41
15	5.8	52, 51	3.3	80	10.7, 10.5	92, 64	3.5	40, 13
17	13.5	73, 84	5.7	48	13.0, 14.3	91, 96	3.0*	18, 12
18	9.3	39, 57	6.0	50	11.5, 7.5	98, 92	2.0*	59, 35
19	10.5	74, 46	3.0	32	14.0, 14.0	83, 71	2.0	9, 25
20	7.1	53, 45	3.3	66	12.7, 12.7	96, 94	1.0	43, 49

Median increase in response = 25 per cent (nominal 95 per cent confidence limits = 9%, 41%).
Median reduction in daily cycles = 1.9 (0.5, 2.7). * Four patients who received oral booster doses daily.

of levodopa. They did not exist before the introduction of the drug, without which parkinsonian patients were in a permanent akinetic off condition. The term 'on-off' is an apt description of the changes which patients experience, but it is unlikely to represent a totally different set of events from those described as 'end-of-dose'. Qualitatively the fluctuations are similar, and the prevalence of both increases with the duration of treatment.

The first part of this study identified some of the reasons for this confusion. Unpredictable fluctuators tend to take more frequent doses at shorter intervals. End-of-dose periods thus become briefer and less often noticed by patients; in some the beneficial effects of consecutive doses overlap and no intervening off period is seen. Some patients have a much longer response latency (60 min or more) than others. Thus supposing a patient usually takes levodopa every 3 h and the mean duration of response is 2½ h with a latency of 1 h: his second dose is taken 3 h after the first, to be followed some ½ h later by 'switching off' before he actually benefits from the second dose, thereby giving the false impression that it is actually responsible for the off period.

The results of the levodopa infusion study indicate that, although patients continued to fluctuate on oral therapy, during infusion their periods of mobility could be extended by over 20 per cent each day and the frequency of on-off cycles markedly diminished. Statistical analysis does not adequately convey the true impact of the infusions. Some patients who had fluctuated wildly and frustratingly five or six times each day for the previous five years were dramatically, albeit for two days only, experiencing continuous, independent mobility for twelve hours or more.

Despite the continuous intravenous administration of levodopa at a constant rate, fluctuations still occurred in some patients. This may have been due to unstable plasma concentration despite the theoretical achievement of an equilibrium between rates of administration and elimination. Examination of preliminary results of plasma levodopa measurements provide some support for this (fig. 2) and more detailed analysis will be published elsewhere.

Four patients (Cases 10, 12, 15, 19) showed an initial brief on period shortly after the start of the infusion on at least one day, which was followed by a brief off period before a sustained response was achieved. Moreover, during the preliminary dose-response study, intermittent clinical benefit was seen in every patient on constant levodopa infusion rates lower than those finally arrived at for the formal part of the investigation. Thus the pharmacological response did indeed appear to be 'all or none', while the thresholds for its initiation and maintenance may be different. This observation would be compatible with Barbeau's (1974) suggestion that there is an oral 'induction dose' for the treatment of Parkinson's disease with levodopa which may be greater than the 'maintenance dose'. It may also be the basis of the observation that occasionally a patient can experience more than one on-off cycle in relation to a single oral dose, and might account for so-called 'yo-yo-ing', since 40 per cent of healthy volunteers show a double peak of absorption after a standard oral levodopa load (Wade *et al.*, 1974; *see also* fig. 2A). We were unable to detect any placebo motor response apart from a momentary flurry of involuntary movements without improvement in function, often provoked by the sight of a needle.

The positive clinical response was identical, whether due to oral or intravenous levodopa or due to parenteral lisuride or apomorphine, indicating that these compounds share similar physiological effects despite differing pharmacological properties. Apomorphine was the first dopamine receptor agonist reported to have antiparkinsonian activity (Cotzias *et al.*, 1970). In the present study it brought about a clear-cut rapid and complete reversal of off phases, confirming the results of other investigators studying both 'predictable' (Düby *et al.*, 1972) and more recently 'unpredictable' (Yahr *et al.*, 1982) fluctuations.

Lisuride is a dopamine-like ergot derivative (Horowski and Wachtel, 1976) which has been shown to have a pharmacological profile in parkinsonian subjects very similar to levodopa and bromocriptine (Schachter *et al.*, 1980). It has the advantage of water solubility and has an immediate beneficial action when administered intravenously to patients from whom levodopa has been withdrawn (Parkes *et al.*, 1981). Unlike apomorphine, however, lisuride effected a more delayed and often incomplete reversal of akinetic periods in our studies. This might reflect the more diverse actions of lisuride demonstrated in experimental animals, since it has inhibitory activity at noradrenaline receptors as well as very high affinity for serotonin receptors, and also for both pre- and postsynaptic dopamine receptors (Kehr, 1977; Fuxe *et al.*, 1978).

Our findings that hesitancy and freezing of gait responded least well to lisuride suggest that the mechanisms of this phenomenon may be different. Intravenous injection of the monoamine precursors levodopa or 5-hydroxy-tryptophan in an acute spinal cat preparation causes the animal to make walking movements when placed on a treadmill, indicating that noradrenaline and serotonin may play a role in stimulating the spinal locomotion centre rather like a starter motor (Shik and Orlovsky, 1976). Dopamine and levodopa are precursors of noradrenaline, itself known to be deficient in certain parts of the central nervous system of parkinsonian patients (Ehringer and Hornykiewicz, 1960; Farley and Hornykiewicz, 1976; Javoy-Agid *et al.*, 1981). Freezing of gait is one of the parkinsonian symptoms most resistant to levodopa therapy, but it has recently been reported that L-threo-dihydroxy-phenylserine (L-threo-DOPS), an alternative noradrenaline precursor, may be useful in its treatment (Narabayashi *et al.*, 1981). Thus certain pharmacological properties of lisuride independent of dopamine agonist activity, such as noradrenaline receptor blockade, may antagonize its own therapeutic benefit.

The results of all three parts of the present investigation are compatible with the notion that the postsynaptic striatal apparatus remains intact and sensitive throughout akinetic off periods. Although we cannot completely rule out the possibility of momentary receptor block, ensuring a continuous supply of the dopamine precursor amino acid or a dopamine receptor agonist can abolish at least the majority of off periods.

The reasons for the development of on-off fluctuations during the course of levodopa treatment remain enigmatic. At the outset all patients have a sustained response to conventional three or four times daily dose regimens. In general, on-off effects develop increasingly over several years of treatment (McDowell *et al.*, 1979). However, they may occasionally be seen within weeks (Cotzias *et al.*, 1969) and even in young patients without idiopathic parkinsonism (Lang *et al.*, 1982).

Whereas pretreatment with a peripheral extracerebral decarboxylase inhibitor might be expected to prolong the elimination of levodopa from plasma, there is considerable doubt as to whether this is actually the case (Morris *et al.*, 1976). The main action of decarboxylase inhibitors is probably at the level of presystemic metabolism (Peaston and Bianchine, 1970; Granerus *et al.*, 1973; Mearrick *et al.*, 1975). Any reduction in the rate of levodopa decarboxylation in the systemic circulation is likely to be accompanied by increased formation of O-methylated and transaminated derivatives (Sandler *et al.*, 1974*b*). The introduction of combined decarboxylase inhibitor-levodopa preparations has failed to reduce the incidence of response fluctuations, which probably emerge earlier on this form of treatment, suggesting that it is swings in brain levodopa concentrations rather than in plasma concentrations which are responsible.

Failure to establish a clear correlation of clinical response with simultaneous plasma concentration indicates a temporal dissociation of the pharmacological effect. True tachyphylaxis does not occur, since maximal effect during on periods is still impressive in severely akinetic patients. Possible long-term alterations in levodopa handling have not been studied in parkinsonian patients on chronic therapy, but preliminary data on plasma levodopa levels in our infusion patients indicates a very rapid distribution phase. If this impression is confirmed, it would suggest that the early phase plasma elimination rate constant may progressively increase on chronic levodopa therapy and might account for the emergence of at least part of the response fluctuations.

Intermittent oral drug therapy gives rise to obligatory fluctuations in plasma drug concentration and perhaps it is surprising that clinical response is ever sustained and stable. The fluctuations in response which develop may represent progressive failure of the central nervous system to act as a transformer, smoothing out amplitude swings of plasma precursor concentrations into a sustained biological response. Since severity and progression of the underlying disease process are not essential for the phenomenon, this failure must be induced by levodopa administration itself.

Subtle cognitive deficits can be detected early in the course of Parkinson's disease, possibly representing dopamine deficiency beyond the nigrostriatal tract in the mesolimbic pathways (Lees and Smith, 1983). It is tempting to speculate that the striking changes in mood described in this study, together with cognitive fluctuations which may also be part of the on-off phenomenon (Delis *et al.*, 1982), as well as the conspicuous variations in motor disability, are all manifestations of intermittent neurotransmitter availability affecting different central dopaminergic systems.

Previous trials of 'slow-release' levodopa preparations were singularly disappointing (Eckstein *et al.*, 1973; Curzon *et al.*, 1973; Sandler *et al.*, 1974*a*), probably because their absorption was delayed and inadequate in the absence of a decarboxylase inhibitor. Our findings indicate that the development of a satisfactory sustained-release formulation of levodopa may be of considerable value in the management of response fluctuations seen in Parkinson's disease.

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CORRELATION OF CORTICAL CHOLINERGIC AND GABA DEFICITS WITH QUANTITATIVE NEUROPATHOLOGICAL FINDINGS IN SENILE DEMENTIA

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SUMMARY

The present paper examines the relationship between choline acetyltransferase (ChAT) activity and gamma aminobutyric acid (GABA) concentrations with neuronal counts, senile plaque counts and estimates of neurofibrillary tangles in a series of 25 cases of senile dementia of Alzheimer type (SDAT) with appropriate controls.

ChAT activity was significantly positively correlated with neuronal counts in the frontal and temporal region for the whole group but not in the demented or control subgroups. Significant negative correlations were also found between plaque counts and ChAT activity in all areas studied in the total group of subjects and in most of the SDAT groups. Significant negative correlations between ChAT activity and estimates of neurofibrillary change occurred in the frontal area and midtemporal gyrus in the SDAT cases. All the above correlations were seen most prominently in the youngest dementia patients (less than 79 years of age) who exhibited the most severe neuropathological and neurochemical deficits. The neurochemical distinction between the young and elderly age group of SDAT cases was well illustrated by the *paradoxical* trends of significantly increased GABA and ChAT levels with increasing age.

The few significant correlations observed between GABA and cell counts were positive and occurred in the temporal lobe in the younger age group. Plaque counts and neurofibrillary tangle estimates showed little correlation with GABA concentrations.

INTRODUCTION

Senile dementia of Alzheimer type (SDAT) is characterized by increased numbers of senile plaques (Tomlinson *et al.*, 1970) and the presence of neocortical neurofibrillary tangles (Tomlinson, 1977). Cerebral volume in female subjects decreases by approximately 18 per cent in SDAT compared with age-matched controls, although the ratio of grey to white matter in the two groups is similar (Miller *et al.*, 1980). There is evidence that the pattern of atrophy associated with SDAT may be age-related (Hubbard and Anderson, 1981).

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Although the cerebral atrophy associated with SDAT is assumed to be due to cortical neuronal loss, few attempts have been made to provide standardized cell counts. Two reports from the same group of workers produced apparently conflicting results. An early study (Terry *et al.*, 1977) suggested that there was no statistically significant difference between cortical neuronal counts in patients with senile dementia and controls. A more recent report (Terry *et al.*, 1981), however, showed a significant reduction in the number of neurons in demented patients compared with controls in the middle frontal region and superior temporal gyrus. The reduction was particularly marked in respect of large neurons. There was no significant correlation between neuritic plaques and cell counts, cortical thickness or brain weight. Our own studies, on a series of 25 SDAT cases, have provided clear evidence of neuronal loss in the frontal and temporal regions (Mountjoy *et al.*, 1983).

Biochemical studies have consistently shown the activity of choline acetyltransferase (ChAT), a marker of cholinergic neurons, to be reduced in post-mortem brain tissue from SDAT patients (Bowen *et al.*, 1976, 1982; Davies and Maloney, 1976; Perry *et al.*, 1977*a*, *b*; Rossor *et al.*, 1980; Wilcock *et al.*, 1982), although a difference in ChAT activity has been demonstrated between younger and older dements (Bowen *et al.*, 1979; Rossor *et al.*, 1981). By contrast, reductions in markers of gamma aminobutyric acid (GABA) neurons are of smaller magnitude and occur only in some cortical areas (Bowen *et al.*, 1976; Perry, 1977*a*; Davies, 1979; Rossor *et al.*, 1982*b*). Attempts to relate biochemical and pathological findings have so far mainly concerned correlations of biochemical values with senile plaque counts, which have been shown to correlate significantly with ChAT activity but not with glutamic acid decarboxylase (GAD), the synthetic enzyme for GABA (Perry *et al.*, 1978). In a later paper Perry *et al.* (1981) again found mean plaque counts to be highly correlated with ChAT activity, possibly with somatostatin and cholecystokinin, and not with GAD. Wilcock *et al.* (1982), however, failed to demonstrate significant correlations between ChAT and plaque counts in the frontal or temporal lobes, but they did show significant correlations for counts of neurofibrillary tangles in the temporal lobe. The present paper examines the relationship between measurements of ChAT activity and GABA concentrations with neuronal counts, senile plaques and estimates of neurofibrillary tangles in a series of 25 SDAT cases with appropriate controls. The data concerning biochemical and neuropathological findings obtained from this material have been published in detail elsewhere (Rossor *et al.*, 1982*b*; Mountjoy *et al.*, 1983) and the present paper is thus concerned only with the comparison of these two sets of results.

METHODS

Full details of the methods are published in Rossor *et al.* (1982*b*) and Mountjoy *et al.* (1983). The comparison was between 25 clinically nondemented and histologically normal subjects and 25 clinically and histologically confirmed cases of dementia of Alzheimer type. In each instance the brain was divided midsagittally, half was reserved for histological examination and the other half frozen for biochemical studies. Cell counts were made with the aid of a Quantimet 720 computerized image analyser and plaque counts or estimates of neurofibrillary change were made as described (Mountjoy *et al.*, 1983).

Biochemistry

The storage procedure and general dissection techniques have been given elsewhere (Rossor *et al.*, 1982*b*). Cortical grey matter was dissected from coronal sections which coincided with the centre of a particular Brodmann area. Tissue samples for biochemical assay were homogenized in water and ChAT activity and GABA content assayed as described (Rossor *et al.*, 1982*b*).

Statistical Analysis

Because the data were not normally distributed, square root transformations were made on the pathological measures and logarithmic transformations were made on the biochemical data to stabilize the variation within groups and to normalize distributions. Pearson correlation coefficients were calculated between the transformed biochemical values and the pathological measurements made in the same Brodmann area in the opposite hemisphere. There were no statistically significant differences between the control and SDAT groups in respect of age, sex or cerebral hemisphere studied (Mountjoy *et al.*, 1983).

RESULTS

Correlations of ChAT Activity with Neuropathological Measures

Neuronal counts. Although there were significant positive correlations between ChAT activity and the number of neurons in the superior, middle and inferior frontal gyri and the superior and middle temporal gyri in the total group (controls + SDAT), there were no significant correlations in either the demented or control subgroups (Table 1). The scatter of the transformed measurements from which the correlations were calculated is illustrated in fig. 1 for Brodmann area 22 and for Brodmann area 9 in fig. 2.

We have previously noted that the ChAT deficit and cortical cell loss in the SDAT group were most marked in the youngest patients (i.e. those aged less than 79 years at death) (Rossor *et al.*, 1982*b*; Mountjoy *et al.*, 1983). The correlation between ChAT activity and neuron counts was thus also estimated in these subgroups.

TABLE 1. CORRELATIONS (PEARSON COEFFICIENT) BETWEEN ChAT AND CELLS IN FOUR CORTICAL COLUMNS

	Brodmann area	*Total group*			*Demented group*			*Controls*		
		r	*n*	*P*	*r*	*n*	*P*	*r*	*n*	*P*
Superior frontal	8	0.358	49	0.012*	0.284	25	0.168	−0.123	24	0.566
Middle frontal	9	0.425	49	0.002*	0.388	25	0.056	−0.005	24	0.982
Inferior frontal	9	0.380	49	0.007*	0.289	25	0.161	0.162	24	0.450
Cingulate	24	0.169	48	0.252	−0.019	23	0.933	−0.218	25	0.295
Superior temporal	22	0.408	50	0.003*	0.375	25	0.065	−0.145	25	0.488
Middle temporal	21	0.327	50	0.020*	0.110	25	0.599	0.229	25	0.270
Inferior temporal	20	0.268	49	0.062	0.280	25	0.175	0.116	24	0.589
Parietal	7	0.327	35	0.056	0.158	19	0.517	0.364	16	0.156
Occipital	17	0.195	49	0.179	0.005	24	0.981	0.211	25	0.311

* $P < 0.05$.

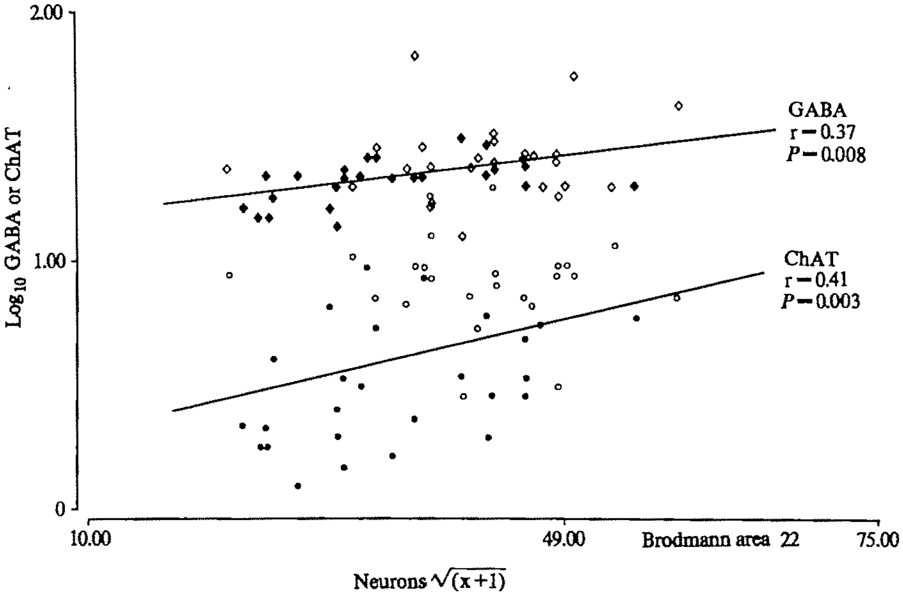

FIG. 1. Scatter of individual log transformed GABA concentrations and ChAT activity plotted against square root transformed neuronal counts in Brodmann area 22. Solid symbols = dementia group; open symbols = controls.

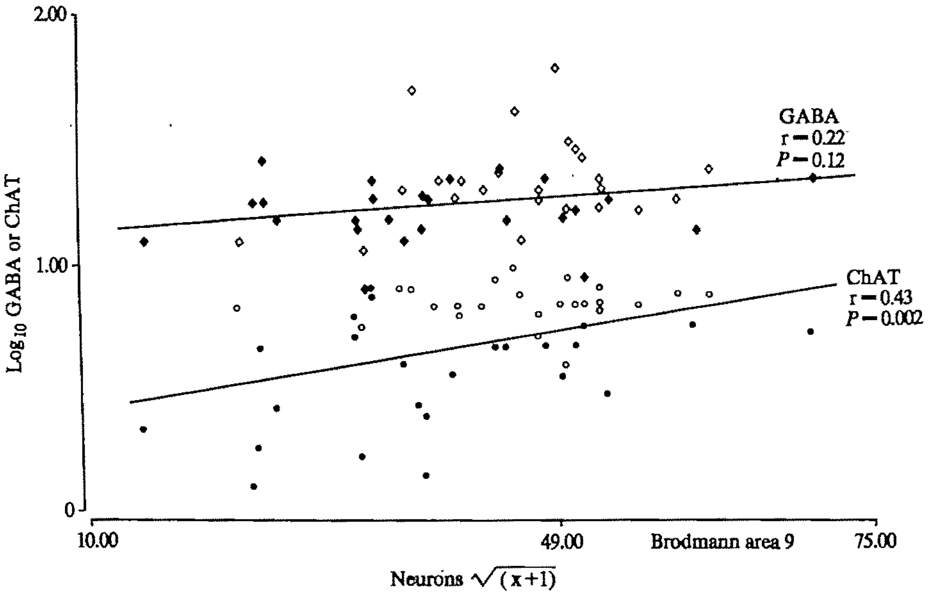

FIG. 2. Scatter of individual log transformed GABA concentrations and ChAT activity plotted against square root transformed neuronal counts in Brodmann area 9. Solid symbols = dementia group; open symbols = controls.

TABLE 2. CORRELATIONS BETWEEN ChAT ACTIVITIES AND CELL COUNTS IN FOUR CORTICAL COLUMNS IN SUBJECTS BELOW 79 YEARS OF AGE

	Brodmann area	*Demented group*			*Control group*		
		r	*n*	*P*	*r*	*n*	*P*
Superior frontal	8	0.677	12	0.016*	−0.070	14	0.811
Middle frontal	9	0.563	12	0.057	−0.105	14	0.722
Inferior frontal	9	0.190	12	0.555	0.160	14	0.584
Cingulate	24	−0.246	11	0.465	−0.382	14	0.177
Superior temporal	22	0.608	12	0.036*	−0.223	14	0.443
Middle temporal	21	0.380	12	0.224	0.343	14	0.230
Inferior temporal	20	0.369	12	0.238	0.365	13	0.221
Parietal	7	−0.017	12	0.959	0.128	14	0.663
Occipital	17	0.257	12	0.419	−0.049	14	0.868

* $P < 0.05$.

Although there were no significant correlations between ChAT activity and neurons in either control or demented subgroups in the elderly patients (> 79 years), SDAT subjects below the age of 79 years did show significant positive correlations between neuron counts and ChAT activity in superior frontal and superior temporal gyri (Table 2).

Plaques. Highly significant negative correlations were observed between plaque counts and ChAT activity for all cortical areas in the total group. The order of correlation is similar to that reported by Perry *et al.* (1978, 1981), but considerably higher than the correlations obtained by Wilcock *et al.* (1982). Significant correlations between ChAT activity and plaques are found in the frontal and temporal regions examined in the demented group, but not in the parietal, cingulate or occipital areas (Table 3). This finding contrasts with that of Wilcock *et al.* (1982) who found no such significant correlations. Correlations for the dementia group alone are not available in the publications of Perry *et al.* (1978, 1981). Although plaque counts were much lower in the control series, significant negative correlations with ChAT activity were nevertheless found in the control group in all three

TABLE 3. CORRELATIONS BETWEEN ChAT ACTIVITIES AND PLAQUE COUNTS

	Brodmann area	*Total group*			*Demented group*			*Controls*		
		r	*n*	*P*	*r*	*n*	*P*	*r*	*n*	*P*
Superior frontal	8	−0.643	49	0.000*	−0.431	25	0.031*	−0.574	24	0.003*
Middle frontal	9	−0.652	49	0.000*	−0.441	25	0.027*	−0.431	24	0.036*
Inferior frontal	9	−0.759	49	0.000*	−0.618	25	0.001*	−0.540	24	0.006*
Cingulate	24	−0.635	48	0.000*	−0.374	23	0.078	−0.102	25	0.627
Superior temporal	22	−0.702	50	0.000*	−0.492	25	0.031*	0.389	25	0.049*
Middle temporal	21	−0.736	50	0.000*	−0.432	25	0.031*	−0.232	25	0.265
Inferior temporal	20	−0.741	49	0.000*	−0.518	25	0.008*	−0.424	24	0.039*
Parietal	7	−0.425	35	0.011*	−0.298	19	0.215	0.129	16	0.634
Occipital	17	−0.458	49	0.001*	−0.101	24	0.640	0.050	25	0.811

* $P < 0.05$.

frontal gyri and in the superior and inferior temporal gyri. An example of the distribution of the transformed plaque counts and the ChAT values in the control and SDAT groups for Brodmann area 22 is illustrated in fig. 3. Interestingly, the significant negative correlation between plaque counts and ChAT activity appears to be most prominent in the younger dementia patients. Correlations between ChAT activity and plaques in the over 79 group showed no significant correlations in the demented subgroup and only a single significant negative correlation in the inferior frontal gyrus in the control group ($r = -0.65$, $P = 0.043$). Table 4 shows the correlations between plaques and ChAT for demented and control subgroups in patients below the age of 79 years. There were no significant correlations in the control group, but significant negative correlations were found in the demented group in the inferior frontal, middle and inferior temporal gyri.

Tangles. ChAT activity values were also compared with neurofibrillary estimates in demented subjects. Controls were omitted from this comparison because they did not exhibit appreciable numbers of neocortical tangles. In the total group of demented subjects significant negative correlations were found in the frontal areas and in the middle temporal region. The correlation for the middle temporal gyrus in the present study ($r = -0.423$) is closely similar to that obtained for counts of neurofibrillary tangles in the temporal lobe ($r = -0.43$) reported by Wilcock *et al.* (1982).

There were no significant correlations when the demented group was divided into subgroups above and below the age of 79.

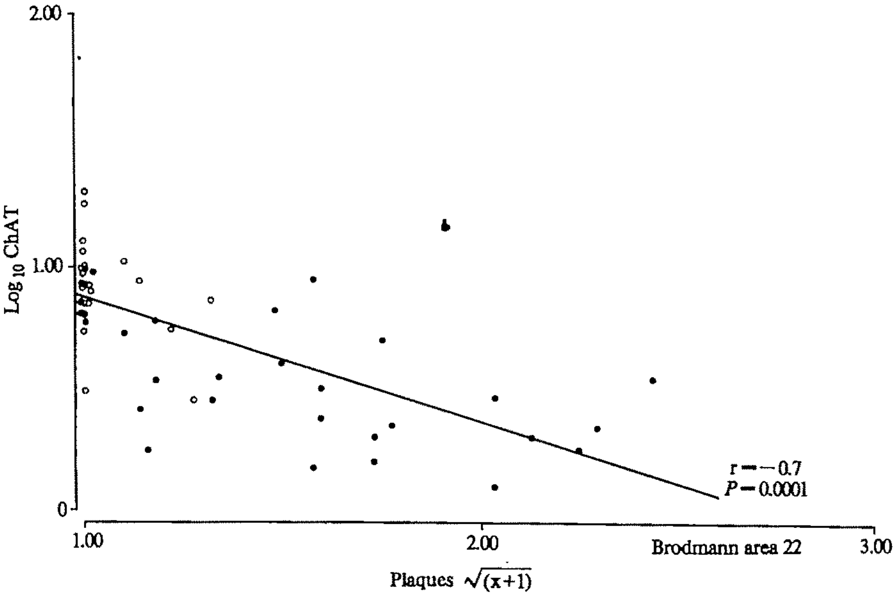

FIG. 3. Scatter of individual log transformed ChAT activity values plotted against square root transformed plaque counts in Brodmann area 22. Solid circles = dementia group; open circles = controls.

TABLE 4. CORRELATIONS BETWEEN ChAT AND PLAQUES IN SUBJECTS BELOW 79 YEARS OF AGE

	Brodmann area	*Demented group*			*Control group*		
		r	*n*	*P*	*r*	*n*	*P*
Superior frontal	8	−0.310	12	0.327	−0.524	14	0.054
Middle frontal	9	−0.557	12	0.06	−0.369	14	0.194
Inferior frontal	9	−0.727	12	0.007*	−0.494	14	0.072
Cingulate	24	−0.227	11	0.503	−0.067	14	0.821
Superior temporal	22	−0.418	12	0.176	0.059	14	0.842
Middle temporal	21	−0.651	12	0.022*	−0.044	14	0.881
Inferior temporal	20	−0.616	12	0.032*	−0.232	13	0.444
Parietal	7	−0.051	12	0.872	−0.256	14	0.374
Occipital	17	0.014	12	0.965	0.131	14	0.656

* $P < 0.05$.

Correlations of GABA Concentrations with Neuropathological Measures

Neuronal counts. Positive correlations were observed between GABA concentrations and neuron counts in the inferior frontal and superior temporal gyri in the total group, in the superior temporal gyrus in the demented group and in the inferior frontal gyrus in the controls (Table 6).

In subjects over the age of 79 years there were only two significant correlations between neuron counts and GABA in the control group (midfrontal, r = 0.64, $P = 0.044$; parietal, r = −0.65, $P = 0.043$). In the SDAT subjects over 79 years of age the only significant correlation between neurons and GABA was in the midtemporal gyrus (r = 0.61, $P = 0.029$).

In subjects below the age of 79 years there were no significant correlations between GABA and neurons in the control group but in the demented group there were three significant correlations: superior frontal (r = −0.59, $P = 0.042$), inferior frontal (r = 0.61, $P = 0.034$) and the superior temporal (r = 0.6, $P = 0.035$). The distribution of the transformed GABA concentration in Brodmann area 22 is illustrated in fig. 1 and for Brodmann area 9 in fig. 2.

TABLE 5. CORRELATIONS BETWEEN ChAT AND NEUROFIBRILLARY ESTIMATES IN DEMENTED SUBJECTS

	Brodmann area	*Total demented group*			*Under 79 years*			*Over 79 years*		
		r	*n*	*P*	*r*	*n*	*P*	*r*	*n*	*P*
Superior frontal	8	−0.529	25	0.007*	−0.276	12	0.385	−0.281	13	0.353
Middle frontal	9	−0.505	25	0.010*	−0.312	12	0.323	−0.341	13	0.254
Inferior frontal	9	−0.417	25	0.038*	−0.312	12	0.323	−0.076	13	0.805
Cingulate	24	−0.222	23	0.309	−0.175	11	0.607	0.345	12	0.272
Superior temporal	22	−0.362	25	0.075	−0.218	12	0.496	−0.163	13	0.594
Middle temporal	21	−0.423	25	0.035*	−0.216	12	0.499	−0.368	13	0.215
Inferior temporal	20	−0.182	25	0.384	0.130	12	0.688	−0.351	13	0.240
Parietal	7	−0.153	25	0.466	−0.160	12	0.619	0.089	13	0.772
Occipital	17	0.150	24	0.483	0.244	12	0.445	0.170	12	0.598

* $P < 0.05$.

TABLE 6. CORRELATIONS BETWEEN GABA AND CELLS IN FOUR COLUMNS

	Brodmann area	*Total group*			*Demented group*			*Controls*		
		r	*n*	*P*	*r*	*n*	*P*	*r*	*n*	*P*
Superior frontal	8	0.160	49	0.271	−0.221	25	0.288	0.345	24	0.099
Middle frontal	9	0.223	49	0.123	0.053	25	0.801	0.187	24	0.381
Inferior frontal	9	0.432	49	0.002*	0.251	25	0.394	0.497	24	0.013*
Cingulate	24	0.165	48	0.263	−0.206	23	0.346	0.253	25	0.222
Superior temporal	22	0.370	50	0.008*	0.514	25	0.009*	0.155	25	0.458
Middle temporal	21	0.243	50	0.089	−0.212	25	0.309	0.391	25	0.053
Inferior temporal	20	0.169	49	0.247	−0.050	25	0.814	0.289	24	0.171
Parietal	7	0.012	49	0.935	0.225	25	0.280	−0.367	24	0.078
Occipital	17	−0.045	49	0.759	−0.360	24	0.084	0.032	25	0.878

* $P < 0.05$.

Plaques. There were no significant correlations between GABA and plaques in the demented or control groups. Division of subjects by age showed no significant correlations in the controls or dements aged below 79 years and a single negative correlation in the demented group over 79 years of age (midfrontal, $r = -0.62$, $P = 0.024$). There were no significant correlations between GABA and plaques in the control group over the age of 79 years.

Tangles. The only significant correlation between GABA and neurofibrillary estimates in the total demented group was in the superior temporal gyrus ($r = -0.53$, $P = 0.006$). There were no significant correlations between GABA and tangle estimates in demented subjects above or below the age of 79 years.

Relationship between age and ChAT and GABA. The correlations between age and ChAT and GABA concentrations in all areas are summarized in Table 7. Fig. 4 illustrates the relationship between age and ChAT and GABA in Brodmann area 22.

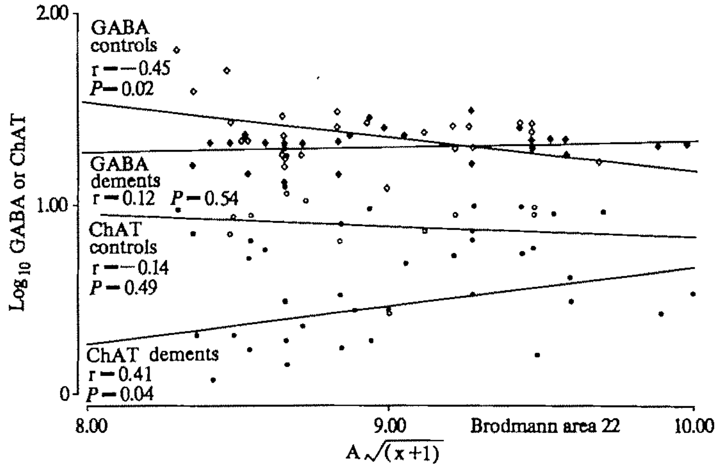

FIG. 4. Scatter of log transformed ChAT activity and GABA concentrations in Brodmann area 22 by diagnosis plotted against square root transformed age. Solid symbols = dementia group; open symbols = controls.

TABLE 7. CORRELATIONS BETWEEN AGE AND ChAT AND GABA CONCENTRATIONS

	Brodmann area	*ChAT Controls*			*ChAT Dementia*			*GABA Controls*			*GABA Dementia*		
		r	*n*	*P*	*r*	*n*	*P*	*r*	*n*	*P*	*r*	*n*	*P*
Superior frontal	8	−0.55	24	0.006*	0.56	25	0.003*	−0.66	24	0.000*	−0.21	25	0.302
Middle frontal	9	−0.36	24	0.088	0.48	25	0.014*	−0.44	24	0.029*	0.11	25	0.585
Inferior frontal	9	−0.36	24	0.088	0.48	25	0.014*	−0.44	24	0.029*	0.11	25	0.585
Cingulate	24	−0.35	25	0.090	0.21	23	0.326	−0.30	25	0.14	0.32	23	0.129
Superior temporal	22	−0.14	25	0.498	0.41	25	0.042*	−0.45	25	0.022*	0.12	25	0.541
Middle temporal	21	−0.30	25	0.14	0.22	25	0.287	−0.48	25	0.016*	0.18	25	0.385
Inferior temporal	20	−0.14	24	0.522	0.14	25	0.507	−0.26	24	0.214	0.20	25	0.331
Parietal	7	−0.31	24	0.135	0.18	25	0.394	0.11	24	0.609	−0.00	25	0.989
Occipital	17	−0.33	25	0.100	0.12	24	0.562	−0.33	25	0.112	0.12	24	0.545

* $P < 0.05$.

There was a tendency for ChAT and GABA concentrations to decrease with increasing age in controls, and there was a significant negative correlation with age in the case of GABA. In dementia, on the other hand, GABA concentrations were higher in older subjects, and ChAT activity also displayed a paradoxical and significant increase with age in areas of frontal and temporal cortex.

DISCUSSION

The reductions in cortical neuron numbers in demented patients in the present series were most marked in the frontal and temporal regions, and most evident in the younger half of the age distribution (Mountjoy *et al.*, 1983). Indeed, we were unable to observe any significant cortical neuron loss in demented patients who died aged over 80 years. The extent of neuronal loss observed in the present series is similar to that reported by Terry *et al.* (1981). The differences between young and old subjects are consistent with the description of pathological differences in SDAT subjects found by Hubbard and Anderson (1981). These authors reported that patients with SDAT, aged less than 80 years, showed pathological cerebral atrophy with global loss of tissue whereas those over 80 years of age generally showed a selective atrophy of the temporal cortex. The differences between young and old subjects in the present study cannot be explained on the basis of faulty diagnosis: all the demented patients had been diagnosed as suffering from dementia in life, and pathologically the elderly demented patients had neocortical tangles and significantly more plaques than control subjects.

Similarly, we have reported previously that the ChAT deficit in the neocortex in SDAT cases is most severe in the youngest subgroup (Rossor *et al.*, 1982*b*). This subgroup of demented patients exhibit a severe ChAT deficit in all areas of neocortex, whereas elderly demented patients have a less severe loss of ChAT activity, which is confined principally to temporal cortex and hippocampus (Rossor *et al.*, 1982*b*).

As the younger demented patients thus show the most severe pathological and neurochemical changes it is perhaps not surprising that the most striking correlations between neuropathological results and biochemical data were observed in the younger subgroup of demented patients. Thus while no correlation could be observed between ChAT activity and neuronal counts in the overall dementia group, significant positive correlations were observed in frontal and temporal lobes in the younger subgroup (Table 2). The highly significant negative correlations between plaque counts and ChAT activity in most cortical areas also appear most strikingly in the younger subgroup of SDAT cases. The correlations observed are of a similar order to those previously described by Perry *et al.* (1978, 1981), despite the fact that their correlations were made using an average plaque count for the whole brain. In this paper the plaque counts in a particular Brodmann area were correlated with measured ChAT activity in the corresponding Brodmann area from the opposite hemisphere of the same brain. Wilcock *et al.* (1982), using an average plaque count for frontal and temporal lobes separately, were unable to show a significant correlation between ChAT activity and plaque formation. They explained the discrepancy between their results and those of Perry *et al.* (1978) by considering the possibility, suggested by Blessed *et al.* (1968), that plaques are subject to a threshold effect, whereby maximum measurable intellectual damage is present at less than maximum level of plaque formation. In our study, negative correlations were also observed between ChAT activity and neurofibrillary estimates in demented patients, but these correlations were only significant for the three frontal and the middle temporal gyri. Our results therefore differ from those from Wilcock *et al.* (1982) in that we show significant correlations between ChAT activity and neurofibrillary estimates in the frontal lobe while they found significant correlations only in the temporal lobe. The correlation that they obtained in their temporal lobe count is very similar to the significant correlation between the neurofibrillary estimate and ChAT activity in the middle temporal gyrus in the present study. It is of interest that the significant correlations between ChAT activity and neurofibrillary estimates and plaque counts in elderly patients are most significant in the temporal lobe, since this agrees with Hubbard and Anderson's pathological observation that it is the temporal lobe which is consistently affected in SDAT and is the only lobe to show atrophy in the older age group of dementias.

The neurochemical distinction between the young and elderly age groups of SDAT cases is well illustrated by paradoxical trends to *increased* GABA and ChAT levels with age in the SDAT group (fig. 4 and Table 7).

The use of GABA as a post-mortem marker is now well established (Spokes *et al.*, 1979). Although it does change rapidly in the initial post-mortem period in animal studies, it is stable over the longer time course of human post-mortem studies and less prone to alteration by agonal factors in the same way as the enzyme GAD. Although reduced GABA concentrations occur in some cortical areas in SDAT cases, the changes are smaller and more circumscribed than those observed for ChAT (Rossor *et al.*, 1982*b*). It is therefore not surprising that a few significant correlations were observed in the present study between cortical GABA values and the neuropathological findings. As might be expected from the fact that GABA is an intrinsic transmitter, the few significant correlations that were observed between it and cell counts were positive. These correlations tended to occur in the temporal lobe, and in the younger age group. Plaque counts and neurofibrillary tangle estimates on the whole showed little correlation with GABA content. Perry *et al.* (1978) also failed to show any significant correlation between plaque counts and GAD activity.

It is now well established from animal studies that the majority of neocortical ChAT activity resides within the nerve terminals of an ascending system of fibres originating from the basal forebrain and there are relatively few intrinsic cortical cholinergic neurons (Emson and Lindvall, 1979). Studies of the distribution of ChAT activity (Rossor *et al.*, 1982*a*, *b*) and cell counts in the nucleus basalis (Whitehouse *et al.*, 1981) indicate that there is a prominent loss of the diffuse cholinergic projection system in the basal forebrain rather than a generalized loss of cholinergic neurons. In this regard, the association between ChAT and the cortical plaque and neuronal counts reported in this paper is of interest although its significance is unclear. Further studies are required to establish the cortical layers in which the main loss of cells occurs. It is possible that the correlation between neuronal counts and ChAT activity reported here is due to both being measures of severity of dementia, rather than to any direct association, and it is certainly premature to consider any causal relation. Similar factors need to be considered in respect of the high correlations between plaque counts, neurofibrillary estimates and choline acetyltransferase activity. Nevertheless, the present findings reinforce earlier conclusions in pointing to the cholinergic deficit as the only neurochemical abnormality so far reported which bears a clear and direct relation to neuropathological indices of the severity of illness in senile dementia of Alzheimer type.

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PSEUDONEGLECT IN A PATIENT WITH PARTIAL CALLOSAL DISCONNECTION

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SUMMARY

Each hemisphere may not only be responsible for processing stimuli from the contralateral sensory systems and for programming movements of the contralateral hand, but may also be important for mediating attention-intention within the contralateral hemispace. If each hemisphere mediates attention-intention within contralateral hemispace, both hemispheres must work in concert especially when an arm is crossed and used in opposite hemispace. If both hemispheres did not work together, the directional bias of each hemisphere would become manifest and induce the contralateral extremity to err toward its own hemispace, inducing pseudoneglect. To test this hypothesis, we examined a patient who had a partial callosal disconnection. In trying visually and somaesthetically to bisect lines with her left hand in right hemispace, the patient made systematic errors to the left; in bisecting lines in left hemispace with her right hand, she made systematic errors to the right. The patient also made less dramatic systematic errors even when a hand was used in its own hemispace, which suggests that each hemisphere mediates attention-intention within and towards the contralateral hemispace.

INTRODUCTION

Under a variety of stimulus and performance conditions, patients with hemispatial neglect may fail to perform activities in the hemispace contralateral to their lesion. When asked to bisect a visually presented horizontal line with their right hand, patients with the hemispatial neglect syndrome bisect the line to the right of actual midpoint, thereby 'neglecting' the left side of the line (Heilman, 1979). This defect cannot be accounted for by a basic sensory disturbance such as hemianopia because not all patients with hemispatial neglect are hemianopic and many patients with hemianopia do not have neglect (McFie *et al.*, 1950).

We have noted that the bisection performance of patients with hemispatial neglect due to right hemisphere lesions is less accurate when the lines are placed to the left side of their body (left hemispace) than when placed on the right side of their body (right hemispace) (Heilman and Valenstein, 1979). Furthermore, ensuring that the line stimulus is seen in the intact right visual field does not appear to affect their performance on the bisection task (Heilman and Valenstein, 1979). Based on these

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observations, we have proposed that patients with hemispatial neglect fail to perform correctly such tasks as line bisection because they have a hemispatial attentional and/or intentional defect (Heilman, 1979; Heilman and Valenstein, 1979).

The hemispatial field is based on an egocentric coordinate system in which the midline of the body or head or both serves as a plane for dividing space into left and right sectors (i.e. a plane perpendicular to a line drawn between the eyes or shoulders or both). Left hemispace refers to the space to the left of the body and/or head midline, and right hemispace refers to the space to the right of body and/or head midlines (Heilman and Valenstein, 1979; Bowers and Heilman, 1980*b*; Bowers *et al.*, 1981). It is not known whether hemispace, as defined by the midline of the torso, differs functionally from that as defined by the head midline (Bauer *et al.*, 1982). For the present discussion, however, hemispace will be viewed in terms of body midline.

Hemispace is not necessarily the same as the visual fields. The visual fields and the hemispace in which the visual fields are aligned *are* synonymous when the eyes fixate on a midline visual stimulus. In this situation, the right visual field falls within right hemispace and the left visual field falls within left hemispace. However, the visual fields and the hemispace in which they fall can be dissociated by having the person fixate on a point to the left or right of midline (Bowers *et al.*, 1981). With fixation to the right, both the left and the right visual fields fall entirely within right hemispace. The converse occurs with fixation to the left of midline (i.e. both visual fields fall within left hemispace).

In a similar manner, the extremities (arms) and the hemispace in which they operate can be dissociated. Each extremity typically operates in its 'own' compatible side of hemispace (i.e. right arm in right hemispace, left arm in left hemispace). By merely placing the arms across the body midline, each arm operates in the opposite 'incompatible' side of hemispace (i.e. right arm in left hemispace, left arm in right hemispace).

The hemispatial field, as we have defined it, may constitute an attentional field as well as a behavioural field (Heilman and Valenstein, 1979; Bowers and Heilman, 1980*b*; Bowers *et al.*, 1981). Attention and intention are psychological constructs related to the manner in which the brain processes and acts on information (Pribram and McGuinness, 1975; Heilman 1979; Bowers and Heilman, 1980*a*). The human brain receives more afferent stimuli than it can process simultaneously. Similarly, although the behavioural repertoire in man is rich, only a limited amount of behaviour can be performed at any one time. Furthermore, some stimuli do not require a behavioural action. The brain mechanisms that prepare the brain for processing sensory stimuli and the mechanisms by which it is decided what to process (i.e. 'select') and how far to process the information is referred to as *attention*. The brain mechanisms by which it is decided whether a stimulus should or should not be acted upon and prepare the brain for action is referred to as *intention*.

Based on these constructs of attention and intention, we have proposed that each hemispace is a perceptual or attentive field for attending to and recognizing stimuli as well as a behavioural or intentional field for acting on or responding to stimuli (Heilman and Valenstein, 1979; Bowers and Heilman, 1980*b*; Bowers *et al.*, 1981). Each hemisphere may not only be responsible for processing stimuli from the contralateral sensory systems and for programming movements of the contralateral hand, but may also be important for mediating attention-intention within the contralateral hemispace.

According to this hemispatial hypothesis, the hemisphere that mediates sensory-motor processing and the hemisphere that mediates attentional-intentional behaviour may be dissociated. For example, consider the situation in which the right arm crosses the body midline and is required to carry out a task in the opposite, incompatible side of hemispace. The left hemisphere receives afferent stimuli and is responsible for programming distal movements of the right arm. However, the right hemisphere is important for mediating attention-intention within left hemispace, where the right arm is located. Thus, when normal persons cross their arms into the incompatible hemispace, the processors that control movements and receive afferent inputs would be mediated by a different hemisphere than the hemisphere that mediates attention-intention within that hemispace (*see* fig. 1). For these sensory, motor, and attentive-intentive processors to be coordinated, interhemispheric communication would be necessary. This interhemispheric communication could be mediated by the corpus callosum, since bihemispheric processing would be required to perform a task in one hemispace when the arms are crossed.

If the hemispheres are disconnected by a callosal lesion, then 'pseudoneglect' would be expected on a line-bisection task. For example, consider the situation in which the right arm of a patient with callosal disconnection is crossed so that the right hand bisects lines in left hemispace. Because of the callosal disconnection, the right arm will not be influenced by the right hemisphere, which is critical for

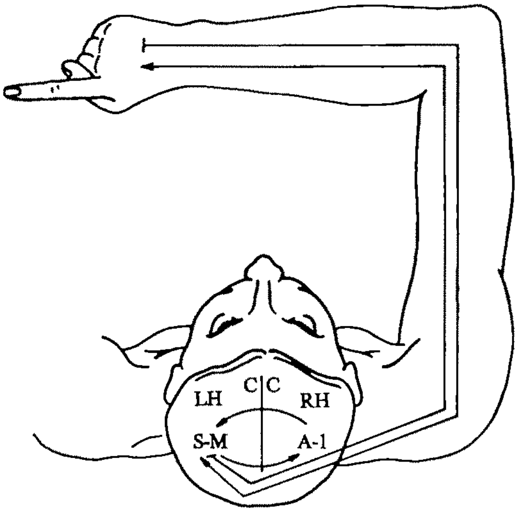

FIG. 1. Arm crossed into the incompatible hemispace. LH = left hemisphere, RH = right hemisphere, CC = corpus callosum, S-M = sensorimotor processors, A-I = attentional-intentional systems.

mediating attention-intention within the left hemispace. The major attentional influences received by the right hand/arm will be from the left hemisphere, which also mediates sensory-motor processing of the right hand. The attentional-intentional systems of the disconnected left hemisphere will therefore direct the sensory-motor apparatus toward the contralateral (right) hemispace. The opposite situation would occur when the left hand bisects lines in right hemispace.

Recently we examined a patient with a partial callosal disconnection induced by an infarction. We performed two line-bisection tasks to investigate the hemispatial attention-intentional hypothesis and also examined normal right-handed subjects on the same tasks.

CASE REPORT

A 43-year-old right-handed woman suddenly experienced severe headache followed by vomiting. She was admitted to the University of Florida's Shands Teaching Hospital where examination revealed neck stiffness. Her blood pressure was 147/98. Initially she had no spontaneous speech, but she repeated complex phrases normally. She followed verbal commands by pointing with her right hand, and she could follow written commands presented in her right visual field but not in the left field. She could pantomime flawlessly with her right hand but not with her left. Her cranial nerves were normal. She had bilateral weakness of her legs, the right being weaker than the left. Strength in her arms was good.

A CT scan showed a haemorrhage in the region of the corpus callosum, extending from the genu to the splenium. Coronal reconstruction showed this to be above the corpus callosum. The following day a cerebral arteriogram did not reveal the cause of the haemorrhage but showed severe spasm of both anterior cerebral arteries. She was considered to have a callosal disconnection syndrome, a severe transcortical motor aphasia and generalized hypokinesia from supplementary motor area involvement, and proximal leg weakness from medial motor cortex ischaemia—all caused by anterior cerebral artery spasm.

Three days after the haemorrhage, in spite of spontaneous orientating to her left, she failed to report all left limb tactile stimuli when stimulated either unilaterally or bilaterally. She continued to exhibit transcortical motor aphasia and was found to be hemialexic, reading 'boat' when presented with the word *houseboat* and 'house' when presented with the word *doghouse*. When blindfolded she could not name objects placed in her left hand. She could, however, pick an object from a multiple choice array (four foils and the correct object). Objects placed in her left hand were manipulated with normal dexterity. She could write single words with her right hand but not with her left. In spite of her inability to perform the simplest pantomimed act to command, to imitate, or to use an actual object with her left hand, she would more often use the left hand rather than the right to scratch her head, wipe her brow, scratch her nose, or rub her eye.

On the fifth day after the haemorrhage, she fluctuated from mutism to transcortical motor aphasia to almost normal linguistic ability. She could write with her right hand, but not with her left, and looked at the pen as if she did not know what to do with it. By day 25 she had consistently regained the ability to name small objects placed in her left hand. She had no drift of her outstretched arms or pseudoathetosis of her fingers. She remained apraxic. She initiated language after a short latency and had excellent comprehension and fluent output. The strength in her lower limbs had improved, and she could stand with assistance. She complained spontaneously 'my two hands fight with each other'.

Forty-four days after the ictus, examination showed that she was alert and orientated, with normal comprehension and language output. She had no signs of hemispatial neglect or extinction. She could write normally with her right hand. Writing with her left hand produced an illegible scrawl. On

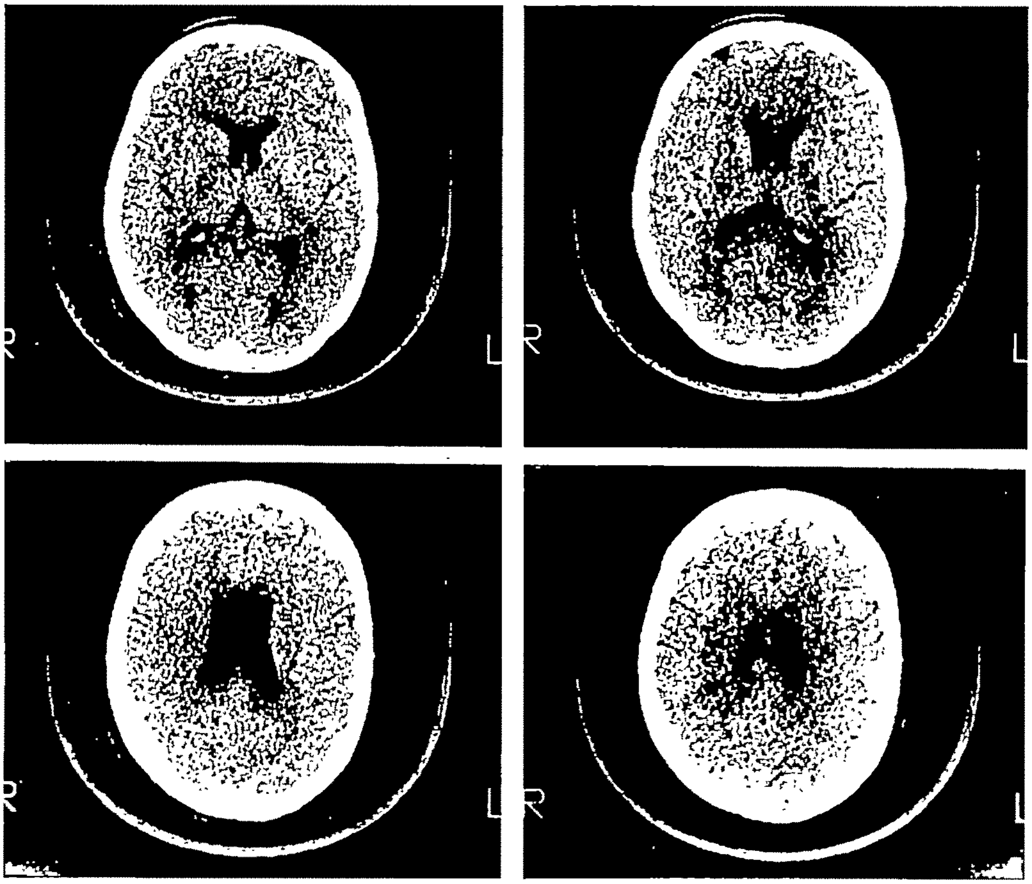

FIG. 2. CT scan of patient showing hypodense area in the region of the body of the corpus callosum.

writing the alphabet with her left hand she also produced only a few recognizable letters, but when copying the alphabet, although it was done with great effort, she showed definite improvement. In spite of this agraphia, when using a typewriter she produced normal sentences using her left hand. With her left hand she slavishly copied a cube that had good visuospatial relationships; with her right hand it was done with motoric ease but was visuospatially incorrect. Praxis testing revealed an ideomotor apraxia of her left hand. She performed worst to pantomime, slightly better with imitation, and best with actual objects.

Horizontal and 35 deg coronal CT scans showed an extensive infarction of the body of the corpus callosum (fig. 2). The most anterior extent of the infarction was at the junction of the genu and body. The posterior one-fourth to one-fifth of the body and all the splenium were intact. There was no cortical involvement, including supplementary and cingulate cortex.

HYPOTHESIS

To test the hypothesis that each hemisphere mediates attention-intention to the contralateral hemispace, we administered two tasks—visual line bisection and tactile line bisection. For each task, the stimuli were placed in either left or right hemispace, and the patient bisected the lines with either the right or left hand. On half the trials her hands were crossed (i.e. right hand bisected lines in left hemispace, left hand bisected lines in right hemispace) and on the remaining trials her hands were uncrossed (i.e. right hand bisected lines in right hemispace, left hand bisected lines in left hemispace).

The following predictions were made regarding the performance of the patient, who was known to have callosal disconnection. (1) Errors to the right of the actual midpoint would be expected when the *right hand* bisects lines placed in left hemispace. This is predicted because the attentional-intentional systems of the disconnected left hemisphere will direct the right arm toward right hemispace. Furthermore, the predicted right-sided errors should be more pronounced when the lines are placed in left than in right hemispace. (2) Conversely, errors to the left of the actual midpoint would be expected when the *left hand* bisects lines placed in right hemispace. Again, this would be predicted because the attentional-intentional systems of the disconnected right hemisphere will direct the left arm toward left hemispace. Similarly, the left-sided errors should be more pronounced when the lines are placed in right than in left hemispace.

METHODS

Subjects

In addition to the patient with the partial callosal disconnection, 24 normal right-handed subjects, ranging in age from 18 to 43 years, were also tested on the two line-bisection tasks.

Stimuli

The stimuli for the visual line-bisection task consisted of straight horizontal lines drawn in black ink on a 20 x 35 cm sheet of white paper. Ten different line lengths were used (14, 16, 18, 20, 22, 24, 26, 28, 30 and 32 cm). These same line lengths were used in the tactile task. The stimuli for this task were constructed by glueing balsa sticks (2 mm in diameter) onto 20 x 35 cm pieces of cardboard.

Procedure

For the visual task, the subjects were instructed to bisect the lines (i.e. 'find the midpoint') using a pen held in either the left or the right hand. For the tactile task, subjects were blindfolded and their index finger was placed on one end of the balsa stick. Half the tactile trials began with the finger being placed on the left end of the stick and half on the right end. The subjects were instructed to find the midpoint after running their finger along the stick. No restriction was placed on how many times the subject could run their finger along the stick.

For both tasks the stimulus cards were placed on a table in either the subjects' left or right hemispace. In the left hemispace condition, the stimulus card was placed so that the right edge of the paper was located 30 cm to the left of body midline. The reverse occurred in the right hemispace condition. While performing the task, the subjects sat with their torso facing straight ahead, although they could turn their head and eyes towards the stimuli located in either left or right hemispace. Thus hemispace was defined in relation to body midline in these tasks.

For both tasks two blocks of 40 trials each were administered to the control subjects, with each block being performed in a different hemispace (right, left). Within each block, the 10 stimulus lengths occurred randomly four times. Half the trials within each block were performed using the left hand,

and half were performed using the right hand. The order of the hemispatial position of the stimuli and the hand used to execute the task was counterbalanced across subjects, so that all combinations of hand and spatial position were obtained for each subject. The two tasks were given in separate sessions with half the subjects receiving the visual line-bisection task first, and half receiving the tactile line bisection first.

The patient was tested using a procedure identical to that of the control subjects, with the exception that two blocks of 20 trials were given in each task. The visual line-bisection task was administered first, and followed a day later by the tactile task. The order of presentation of the trials for the visual task was: right hand-right hemispace, left hand-left hemispace, left hand-right hemispace, and right hand-left hemispace. The presentation of trials for the tactile task was in the reverse order.

RESULTS

Visual Line-Bisection Experiments

A repeated measures analysis of variance (ANOVA) was performed on the visual line bisection data for the control group with hand (left, right) and hemispace (left, right) as within-subject factors. The results of this analysis disclosed neither significant main effects for hand ($F_{1,23} = 2.6$, $P = 0.12$) or hemispace ($F_{1,23} = 1.6$, $P = 0.22$), nor a significant interaction between these factors ($F_{1,23} = 0.07$, $P = 0.78$). Although the results of the ANOVA suggested that line-bisection performance did not differ between the two hands *per se*, nor between the two hemispaces in which the task was carried out, it did not provide information as to whether bisection performance by the two hands in each hemispace differed significantly from the actual midpoint of the line to be bisected. To assess this, we subsequently performed t tests which indicated that bisection performance in each of the hand-hemispace conditions did not significantly differ from the actual midpoint (right hand-right hemispace = 0.08 cm to the right, $t = 0.64$, $P > 0.05$; right hand-left hemispace = 0.09 cm to the left, $t = 0.12$, $P > 0.05$; left hand-right hemispace = 0.10 cm to the left, $t = 0.98$, $P > 0.05$; left hand-left hemispace = 0.23 cm to the left, $t = 1.6$, $P > 0.05$). Thus the control group performed almost flawlessly, and their performance across the various hand-hemispace conditions is depicted in fig. 3.

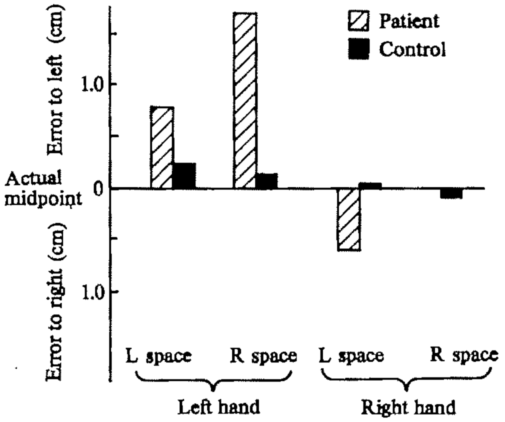

FIG. 3. Mean errors on visual line-bisection task by patient and 24 normal controls using left and right hands across left and right hemispace.

In contrast, the patient made significant and systematic directional errors on visual line bisection. The results of the ANOVA of her data revealed that performance by the left hand ($\bar{X} = 1.2$ cm) differed significantly from that of the right hand ($\bar{X} = 0.3$ cm) ($F_{1,9} = 36.6$, $P = 0.0002$). Likewise, performance in left hemispace ($\bar{X} = 0.1$ cm) differed significantly from that in right hemispace ($\bar{X} = 0.8$ cm) ($F_{1,9} = 9.2$, $P = 0.01$). Again, t tests were subsequently carried out to determine whether performance by the hands in each of the hemispace conditions differed significantly from the actual midpoint of the line to be bisected. They yielded the following conclusions. (1) The patient erred significantly to the left of actual midpoint when the left hand bisected lines placed in either right hemispace ($\bar{X} = 1.7$ cm, $t = 6.5$, $P < 0.05$) or in left hemispace ($\bar{X} = 0.8$ cm, $t = 2.5$, $P < 0.05$). A subsequent analysis indicated that these errors to the left were significantly greater when the line-bisection task was carried out in right than in left hemispace ($t = 3.4$, $P < 0.05$). (2) The patient erred significantly to the right of actual midpoint when the right hand bisected lines placed in left hemispace ($\bar{X} = 0.6$ cm, $t = 2.6$, $P < 0.05$). No systematic directional errors were made by the right hand when bisecting lines in right hemispace ($\bar{X} = 0.01$ cm to the right, $t = 0.16$, $P > 0.05$). In general, the left hand made directional errors to the left and the right hand made directional errors to the right; these findings are depicted in fig. 3.

A direct statistical comparison between the visual line-bisection performance of the patient and that of the control subjects is not appropriate because of the absence of between-subjects variability in the data of the patient. However, her performance across each of the hand and the hemispace conditions was converted into standard deviations (SD) from the mean performance of the control subjects across each of these conditions. Her scores were 1.2 SD from the mean of the control group in the left hand-left hemispace condition, 4.0 SD from the mean in the left hand-right hemispace condition, 0.1 SD from the mean in the right hand-right hemispace condition, and 1.6 SD from the mean in the right hand-left hemispace condition.

Tactile Bisection Experiments

The results of the ANOVA of the tactile bisection data for the control subjects revealed that bisection performance in left hemispace ($\bar{X} = 0.34$ cm to right) differed significantly from that in right hemispace ($\bar{X} = 0.77$ to left) ($F_{1,23} = 30.2$, $P < 0.01$). A significant interaction between hand and hemispace also occurred ($F_{1,23} = 7.33$, $P < 0.01$) and *post hoc* comparisons using Duncan's procedure revealed that left hand bisections differed significantly in left *versus* right hemispace (left hemispace = 0.18 cm to right, right hemispace = 0.83 cm to left, $P < 0.05$). Likewise, right hand bisections differed significantly in left *versus* right hemispace (left hemispace = 0.5 cm to right, right hemispace = 0.72 cm to left, $P < 0.05$). Within left hemispace, the left hand ($\bar{X} = 0.18$ cm to right) differed significantly from the right hand ($\bar{X} = 0.50$ cm to right, $P < 0.05$). However, within right hemispace, the two hands did not differ from each other (left hand = 0.83 cm to left, right hand = 0.72 cm to left, $P > 0.05$).

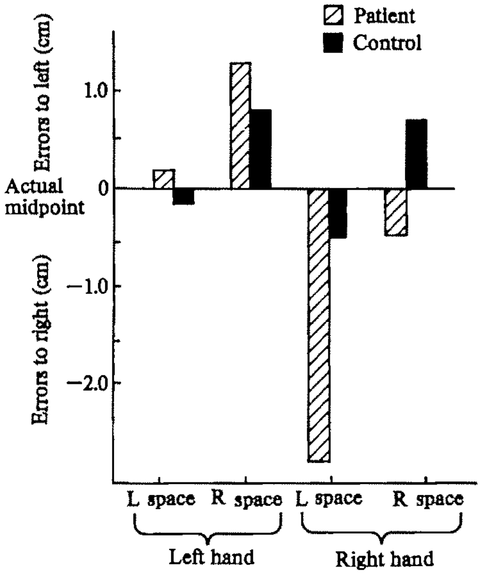

FIG. 4. Mean errors on tactile line-bisection task by patient and 24 normal controls using left and right hands across left and right hemispace.

To determine whether the accuracy of each hand in each hemispace differed significantly from the actual midpoint of the line to be bisected, we made further *post hoc* comparisons. Results of these t tests indicated that in left hemispace the left hand did not differ from the actual midpoint (t = 1.11, $P > 0.05$), although the right hand erred significantly to the right of the actual midpoint (t = 2.9, $P < 0.05$). In right hemispace, bisection performance by each hand was significantly to the left of the actual midpoint (left hand, t = 4.8, $P < 0.05$; right hand, t = 5.1, $P < 0.05$). These findings, depicted in fig. 4, have been previously reported by Bowers and Heilman (1980*b*) and interpreted in terms of the contribution of hemispheric-hemispatial mechanisms and anatomical pathway-transmission models for producing laterality effects in normal subjects.

In contrast, the patient showed a different pattern of asymmetries on the tactile line-bisection task. The results of the ANOVA of her data revealed that performance by the left hand ($\bar{X}$ = 0.5 cm to left) differed significantly from that of the right hand ($\bar{X}$ = 1.2 cm to right; $F_{1,9} = 17.4$, $P < 0.05$). Likewise, performance in left hemispace ($\bar{X}$ = 1.4 cm to left) differed significantly from that in right hemispace ($\bar{X}$ = 0.4 cm to right, $F_{1,9} = 9.3$, $P < 0.05$). Again, t-tests were subsequently carried out to determine whether performance by the hands in each of the hemispace conditions differed significantly from the actual midpoint of the line to be bisected. The results of these analyses were as follows. (1) The patient erred significantly to the left of the actual midpoint when the left hand bisected lines in right hemispace ($\bar{X}$ = 1.3 cm, t = 3.6, $P < 0.05$). No systematic directional errors were made by the left hand when bisecting lines in its own left hemispace ($\bar{X}$ = 0.2 cm to left, t = 0.88, $P = 0.44$). (2) The patient erred significantly to the right of the actual midpoint when the right hand bisected lines in left hemispace ($\bar{X}$ = 2.9 cm, t = 3.2, $P < 0.05$). Again, no systematic directional errors were made by the right hand when bisecting lines in its own right hemispace ($\bar{X} = 0.5$ cm to right, $t = 1.9$, $P > 0.05$). Thus, the left hand made directional errors to the left when bisecting lines in right hemispace (thereby deviating toward its own hemispace). Similarly, the right hand made directional errors to the right when bisecting lines in left hemispace (thereby deviating toward its own hemispace). These findings are depicted in fig. 4.

Again, because direct statistical comparison of the control subjects and the patient was not appropriate, the performance of the patient across each of the hand and hemispace conditions was transformed into standard deviations from the mean performance of the control subjects in each of the hand-hemispace conditions. Her scores were 0.5 SD from the mean of the control group in the left hand-left hemispace condition, 1.0 SD from the mean in the left hand-right hemispace condition, 1.3 SD from the mean in the right hand-right hemispace condition, and 5.8 SD from the mean in the right hand-left hemispace condition.

DISCUSSION

The results of the two line-bisection tasks indicate that the patient with partial callosal disconnection showed a striking 'pseudoneglect' phenomenon that was most apparent when the line stimuli were placed in one hemispace and a 'crossed' hand was required to execute the task. That is, the right hand made errors to the right when the task was performed in left hemispace, and the left hand made errors to the left when the task was performed in right hemispace. These findings suggest that the patient had a bilateral hemispatial defect induced by her partial callosal lesion. Specifically, each hand appeared to deviate toward its own hemispace, and this was most apparent when the hand was required to operate in the contralateral hemispace.

Several neuropsychological mechanisms might account for the errors made by the patient on the line-bisection tasks. Smith and Latto (1982) and De Renzi *et al.* (1982) have suggested that patients with hemispatial neglect may have oculomotor disorders. It is possible that some of the symptoms of 'pseudoneglect' in the present patient may be related to similar oculomotor mechanisms. When the patient was required to bisect a line visually, the hemisphere contralateral to the hand performing the task became activated, inducing contralateral head and eye deviation. For example, head and eye deviation to the left (right hemisphere activation) would occur when the left hand was required to perform the task. With such deviation to the left the right side of the line may not have been seen. The part of the line not seen would not be bisected. In addition, even if the entire line was seen, the larger part of the line would fall in the right visual field. Because of the callosal disconnection, the afferent stimuli from the right visual field to the left hemisphere would have no access to right hemisphere motor systems of the left hand. The left hand would consequently bisect only that portion of the line stimulus seen in the left visual field, resulting in dramatic directional errors to the left. The opposite would occur with right hand performance. There are two major difficulties with these hypotheses. At the time of this testing the patient did not have a splenial lesion, either anatomically or functionally, so that visual stimuli coming into one hemisphere had access to the other hemisphere. Secondly, both of these visual hypotheses cannot account for the patient's performance on the tactile task, which required no visual input.

A second hypothesis to account for the patient's performance relates to the representational map hypothesis of Bisiach and Luzzatti (1978), which is similar to Brain's (1941) idea of the body schema. Bisiach and Luzzatti (1978) asked two patients with neglect from right hemisphere damage to describe from memory a highly familiar scene. In one condition they were to take the perspective of facing a cathedral located at the end of the plaza. In a second condition they were to take the perspective of facing away from this cathedral. In the patients' descriptions, left-sided details were omitted depending on the perspective taken. On the basis of these findings and those from a subsequent study (Bisiach *et al.*, 1979), these investigators postulated that mental representation of the environment is structured topographically and seems to be mapped across the brain. That is, the processes by which visual image is conjured up may be split between the two hemispheres (like the projection of a real scene), and with right hemisphere damage there is a representation disorder for the left half of this image.

The representational map postulated by Bisiach and Luzzatti (1978) may be organized hemispatially so that left hemispace is represented in the right hemisphere and right hemispace is represented in the left hemisphere. When the hand of a callosally disconnected patient must work in the opposite hemispace, it may be disconnected from the mental representation of that hemispace. Although this hypothesis may explain why our partially disconnected patient made greater errors when each hand was used in the opposite hemispace, it cannot account for the systematic directional errors made by each hand toward its own hemispace. This hypothesis also cannot explain why our patient made errors even when the arms were uncrossed and operating in their own 'compatible' hemispaces.

A third hypothesis to account for the patient's 'pseudoneglect' on the line-bisection task is that she had a hemispatial attentional-intentional defect with an associated directional hypokinesia, similar to that observed in patients with hemispatial neglect (Heilman *et al.*, 1983*a*). If each hemisphere is important for mediating activation-intention within and towards the contralateral hemispace independent of limb used, then callosal disconnection should result in each limb erring towards its own hemispace. This is because when the limb executing behaviour is in the opposite side of hemispace, the hemisphere important for directing attention-intention into the contralateral hemispace would be disconnected from the hemisphere important for controlling sensory-motor processing of the limb.

Support for the hemispatial aspect of the defect in neglect has been based on line-bisection performance in these patients. Hemispatial neglect is not significantly improved when the patients are required initially to attend to and name letters located on either end of the line to be bisected. However, performance is significantly worse when the lines are placed in left rather than in right hemispace (Heilman and Valenstein, 1979).

Although the present patient made the greatest line-bisection errors when a hand was used in opposite hemispace (right hand-left hemispace; left hand-right hemispace), errors were also made, but to a lesser extent, by each hand in its own hemispace. Each hemisphere may intend directionally towards contralateral hemispace (Kinsbourne, 1970*b*), but in normal subjects this hemispheric directional intention may be counteracted by the other hemisphere. Thus, profound directional errors are not present in normal subjects. However, with a callosal disconnection or a destructive lesion of one hemisphere, this directional intention of one hemisphere may be unopposed, resulting in systematic directional errors—even when an extremity is used in its own hemispace.

Further support for a directional intentional defect in patients with neglect, as well as the present patient, comes from two recent studies. In performing a midline pointing task (Heilman *et al.*, 1983*b*), blindfolded subjects were asked to put their index finger on the centre of their chest (midline of sternum) and then to extend their arm fully and point to an imaginary point in space directly in front of the middle of their chest. Patients with neglect—using their right hand to point—made profound errors to the right of the actual body midline, whereas patients with left hemisphere damage (using the left hand) and normal controls (using either the left or right hand) erred slightly to the left of the actual body midline. For example, normal controls using the right hand erred to the left ($\bar{X} = 1.1$ cm) and using their left hand they erred to the left ($\bar{X} = 0.8$ cm). In contrast, the callosally disconnected patient made profound errors to the right when pointing with her right hand ($\bar{X} = 12.3$ cm) and profound errors to the left when pointing with her left hand ($\bar{X} = 14.5$ cm). Her abnormal performance on this task cannot be explained by sensory, attentional, exploratory, or gaze defects.

In another study, we examined the ability of patients with left-sided hemispatial neglect to move a simple lever either towards or away from the neglected hemispatial field. In some conditions the lever was moved towards left hemispace, and in other conditions the lever was moved towards right hemispace. On this task, patients showed evidence of a directional hypokinesia, that is, they took longer to initiate movements towards the neglected left hemispace than towards the nonneglected right hemispace. Directional asymmetries were not found in control subjects (Heilman *et al.*, 1983*a*).

It is difficult to attribute this patient's 'pseudoneglect' on the visual line-bisection task entirely to hemispatial and directional intentional defects. Since the patient's splenium was intact, both hemispheres should have received visual feedback that her line-bisection performance was grossly inaccurate.

Although previous studies have suggested that 'intentional' mechanisms may, in part, contribute to hemispatial and directional effects, this does not preclude the role of 'attentional' mechanisms. Attention and intention are closely linked, in that typically action is only taken on information that is attended, although dissociations can occur. Since the manner in which attentional effects are inferred is usually based on behavioural indices that are also measures of intention, defective attentional mechanisms could be overtly manifested and interpreted as defective intention. Each hemisphere could be important for mediating attention within and towards the contralateral hemispace, regardless of whether each hemisphere also mediates hemispatial and directional intention. The right hemisphere attends better to stimuli in left hemispace, displaying a leftward attentional bias as suggested by Kinsbourne (1970*a*), whereas the left hemisphere better attends to stimuli in right hemispace, displaying a rightward attentional bias. A callosal lesion could theoretically disrupt the interhemispheric mediating influences of these directional hemispatial attentional biases: when the right hand of a callosally disconnected patient bisects a line, attention is directed towards the right. The left side of the line is not fully attended or processed and does not affect behaviour. The opposite could occur when the left hand is used.

ACKNOWLEDGEMENT

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THE HEMI 3 SYNDROME

HEMIHYPERTROPHY, HEMIHYPAESTHESIA, HEMIAREFLEXIA AND SCOLIOSIS

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SUMMARY

Three unrelated girls presented with a developmental syndrome of hypertrophy involving half or a quadrant of the body and not involving the face. The appearance was one of inappropriately large size of the affected side rather than contralateral atrophy. On the larger side, there was hypertrophy of muscle and increased power as well as an increase in diameter, but not in length, of long bones. There was areflexia and decreased pain and temperature sensation on that side. The patients also had progressive scoliosis and foot deformities on the enlarged side.

One patient had a lumbar myelomeningocoele, and all 3 had a family history of neural tube closure defects. EMG, nerve conduction studies, EEG, skull x-rays, PEG, and cerebral CT scans were normal. Myelography did not demonstrate an enlarged cord, and in particular there was no evidence for syringomyelia. Chromosome studies revealed normal karyotypes. Sex chromatin was female on both sides in one patient.

A defect of the dorsal lip of the neural tube or the neural crest is postulated to explain the abnormality. The association with closure defect in one patient and a positive family history of other neural tube defects in all 3 patients suggests that the developmental defect occurs at an early embryonic stage.

Recognition of the syndrome is important. It can be distinguished clinically from hemiatrophy of cerebral origin. The neurological abnormalities are static, but the scoliosis is progressive and requires correction. The condition is associated with an increased prevalence of neural tube closure defects in the family, and forms part of a spectrum of genetically and embryologically related CNS malformations with multifactorial inheritance. Probands, parents, siblings and parents' siblings should be counselled that the risks of spina bifida and anencephaly in their offspring are the same as those in relatives of probands with classical neural tube defects, and should be offered prenatal diagnosis.

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INTRODUCTION

Twenty years ago we saw a young girl with hemihypertrophy whose normal side was appropriate in strength and appearance for her sex, whereas the hypertrophic side was thicker and somewhat shorter. Over the years it became apparent that she had areflexia and sensory loss on the affected side, and she also developed a progressive scoliosis. Description of a similar case by Fox and Huott (1974) confirmed that this was not a unique occurrence, and we have since studied two other patients with this syndrome. From a morphogenetic point of view, the disorder appears to be related to a defect in closure of the neural tube, and this, together with the clinical findings, suggests an abnormality of the neural crest on the affected side.

CASE REPORTS

Case 1

A 26-year-old right-handed woman was the fifth of 8 children. She was the product of a normal pregnancy, but delivery was prolonged with breech presentation and required forceps assistance. Her parents noticed that the two sides of her body were unequal and at the age of 14 months examination suggested that she had right-sided hemiatrophy. Gradually, however, it became clear that the right side was normal and the left hypertrophied.

As she matured it became apparent that she was developing severe scoliosis and at the age of 13 years, investigations were undertaken to determine its cause. The child experienced multiple bruises, cuts and burns on the left side of her body but did not appreciate pain, in contrast to her unaffected side. She used her right hand for eating and writing, but was much stronger with the left.

She was of short stature (155 cm) with an obvious scoliosis. It was dorsal and left convex, well defined, extending from T1 to T12 and it was only partially correctable on left lateral bending. Secondary or right convex cervicothoracic and thoracolumbar curves were present which were partially correctable on right lateral bending. The scoliosis measured 28 to 30 deg in both upright and supine positions. The blood pressure and pulses were symmetrical and normal. There were no abnormal cutaneous lesions except for burn scars from a heating pad on the left side of her back. The left limbs appeared bulky, short (shortening of 1.3 cm of the femur, 0.8 cm of the tibia, 1.5 cm of the humerus and 1 or 2 mm of the radius), and somewhat masculine (fig. 1A, C, D). There was a severe hallux valgus deformity of the left foot (fig. 1A, D). Mental status and the cranial nerves were normal. There was no facial asymmetry. Stretch reflexes were absent in the left arm and leg, and normal in the right. Tone was symmetrical and normal, whereas strength was superior on the left side and normal on the right. An equivocal plantar response on the right was noted on numerous occasions. There was decreased pain and temperature sensation from the C2 dermatome downwards on the left side; other sensory modalities were normal.

Radiological examination, including myelography, skull x-rays and pneumoencephalography, were normal. There were no structural abnormalities of the spine. The long bones of the left arm and leg were found to be shorter and thicker radiologically, confirming the clinical measurements. Motor and sensory nerve conduction and EMG studies, sweat tests, skin fibroblast cultures of both arms to exclude mosaicism, and leucocyte karyotypes were normal.

By 18 years of age, the scoliosis worsened and a corrective procedure using Harrington rods was carried out. The patient was reexamined at 26 years of age (fig. 1B–D). She had trained and was working as a registered nurse. Her examination remained unchanged and the neurological deficit appeared to be static. Limb circumferences were as follows. Upper arm: right, 20.2 cm, left, 23 cm; midforearm: right, 13 cm, left, 16.5 cm; midthigh: right, 41.2 cm, left, 45 cm; midcalf: right, 28.9 cm, left, 30.2 cm.

The family was of French Canadian and Irish ancestry, and there was no known parental consanguinity. The pedigree (fig. 3, Family P) revealed a younger sister with a lumbar meningomyelocoele and paraplegia, and a brother with a branchial cyst. One nephew had congenital clubfeet, and another was stillborn with renal agenesis and polydactyly. A maternal first cousin also had polydactyly.

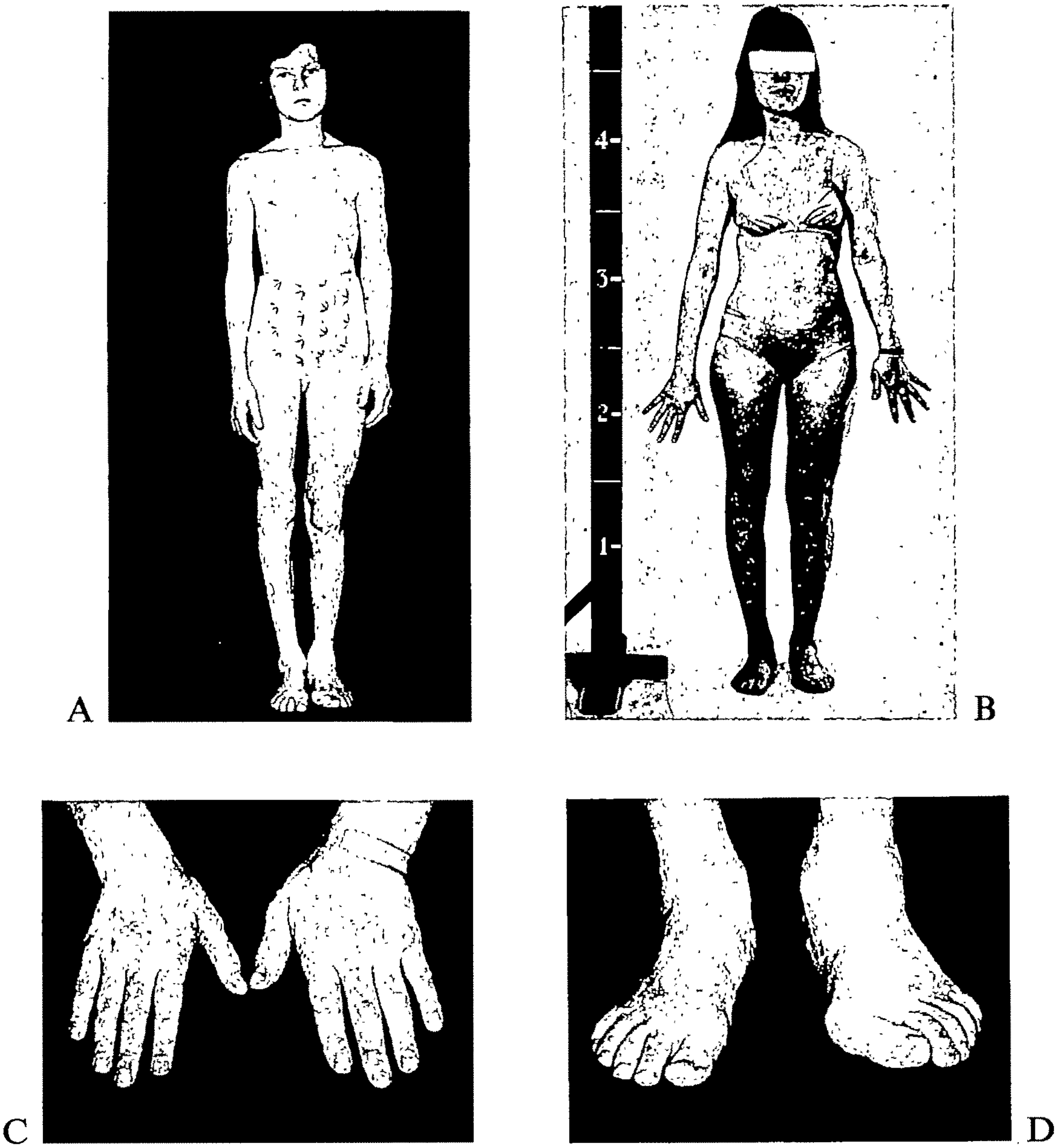

FIG. 1. A, *Case 1* at age of 13 years. Note the thicker but shorter left upper and lower extremities. B, same patient at the age of 26 years. C and D, views of the larger left hand and foot, compared with the right.

Case 2

This right-handed girl came to medical attention as an infant because of a 'congenital clubfoot' on the left which was corrected by three surgical procedures. As she matured, it became clear that the left side of her body was larger and bulkier than the right. She developed a progressive scoliosis. She had no pain sensation on the left and was unable to differentiate warm from cool water although she was able to perceive extremes of temperature. She had to test the bath water with her right hand or foot. She was of average intelligence.

At the age of 12 years she was investigated because of her progressive scoliosis. This was thoracic, convex to the left, and she had a gibbus to the left of 2 cm. She had a compensatory right lumbar scoliosis with a gibbus of 1.5 cm. She was balanced with the left shoulder higher than the right. She was a short, slender girl with inappropriately large extremities on the left (fig. 2). There were old scars from burns and cuts on the left limbs that were notably absent from the right. Facial features, hair and skin were normal. The cranial nerves were normal and there was no clear facial asymmetry. The left limbs were shorter (femur 0.6 cm and tibia 1.7 cm on scanograms), bulkier, and of superior strength for a girl of her age. She had a cavovarus deformity of the left foot. Tone was symmetrical and normal. There were no abnormalities of sweating or vascular changes. The tendon reflexes were absent on the left and normal on the right. Pain and temperature sensation was diminished from the C2 dermatome downwards on the left, whereas other sensory modalities were normal. Laboratory investigations, including radiological examination of the skull, CT scan of the head, myelography and motor and sensory nerve conduction studies, were normal. She had thoracic scoliosis of 51 deg from T6 to T11 with a lumbar scoliosis of 32 deg from T12 to L4.

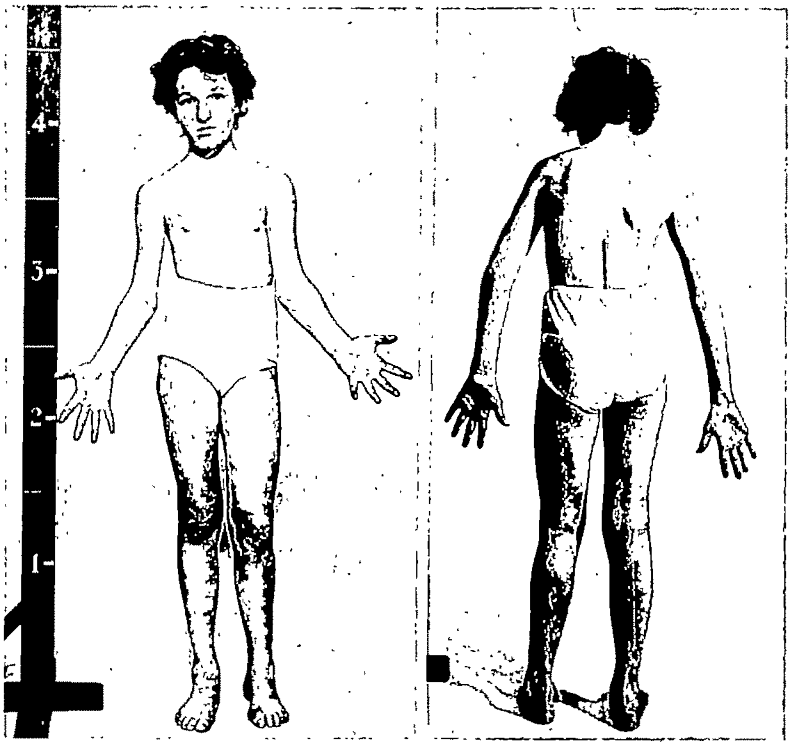

FIG. 2. *Case 2.* Note the increased bulk of the left upper and lower limbs and the scoliosis.

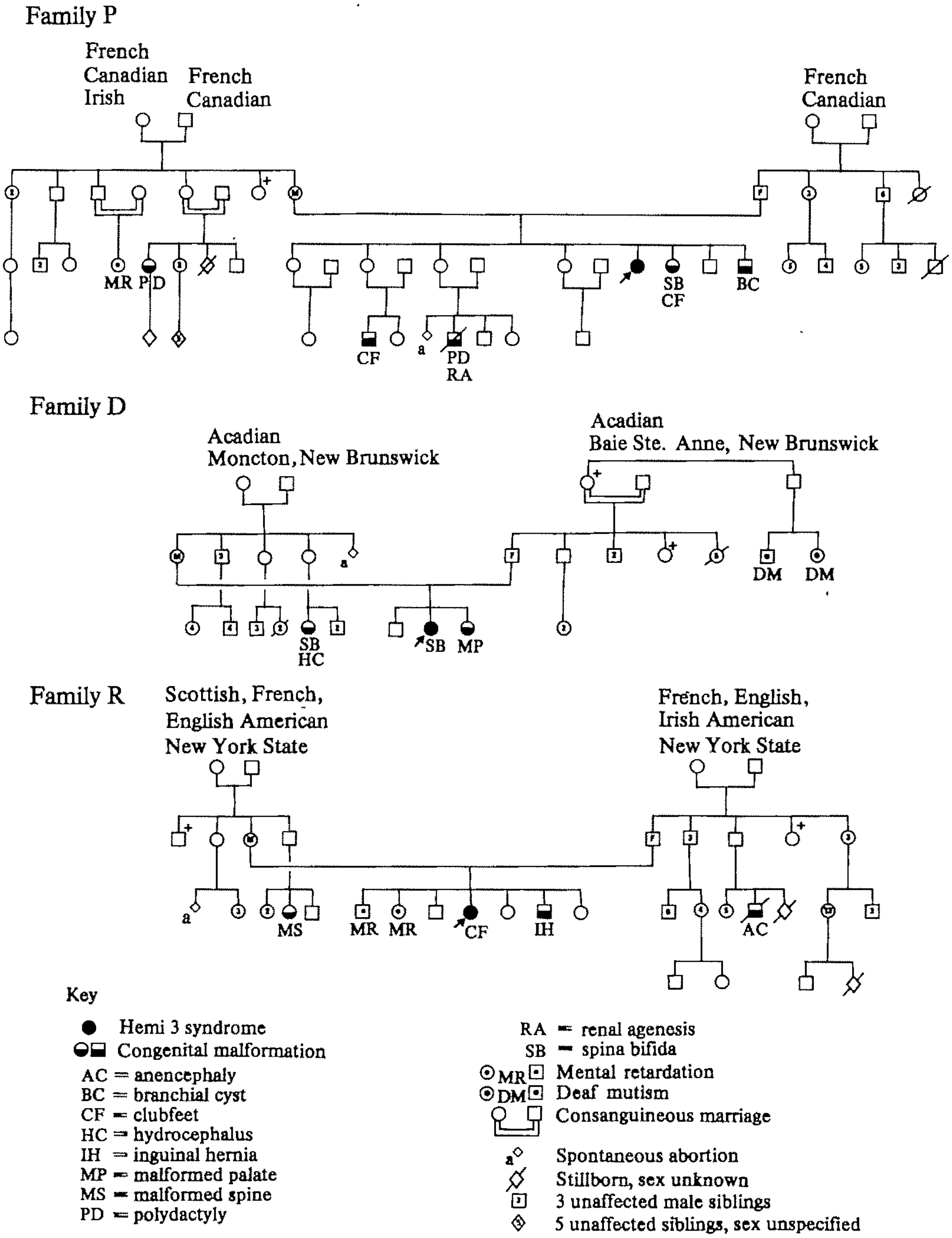

FIG. 3. Pedigrees of Case 1 (Family P), Case 3 (Family D), and Case 2 (Family R). All 3 families have members with dysraphic conditions.

The patient was the fourth of seven children, born to unrelated parents of mixed English, French, Irish, and Scottish American ancestry (fig. 3, Family R). The patient's two oldest siblings were retarded. A paternal first cousin was stillborn with anencephaly. A maternal first cousin had a spinal malformation, and was treated for scoliosis. No-one in the family was known to have hemihypertrophy.

Case 3

A 12-year-old right-handed girl was born with a high lumbar meningomyelocoele. This was repaired at 5 months of age and she had a mild residual spastic paraparesis. Her left upper quadrant was larger than the right, and she developed a slowly progressive scoliosis. She was able to walk without difficulty but could not run.

She was of normal intelligence and had no hydrocephalus. There were no abnormalities of skin, hair or pigmentation. Examination revealed severe thoracic scoliosis convex to the left between T3 and T10 of 78 deg. She had a right convex thoracolumbar scoliosis between T10 and L3 of 105 deg. There was decreased sweating of the left upper quadrant. The left pupil was smaller than the right, but reactive. Other cranial nerves were normal. She was areflexic with increased bulk and strength in the left upper quadrant, whereas the reflexes, size, and strength of the right arm were normal. There was decreased pain and temperature sensation from C2 to T7 on the left side. She had a paraparesis with bilateral extensor plantar responses. Radiographs of the spine showed spina bifida from L3 downwards, including the sacrum.

The patient was the second of three children of unrelated Acadian parents from New Brunswick (fig. 3, Family D). Her younger sister had a malformation of the palate, and a maternal first cousin had spina bifida and hydrocephalus.

DISCUSSION

These 3 patients manifest an unusual clinical constellation, namely, hemihypertrophy with ipsilateral areflexia, pain and temperature loss, and progressive scoliosis.

Hemihypertrophy is the overgrowth of all constituents on one side of the body. It may be congenital or acquired, limited or extensive, as classified by Ward and Lerner (1947). This syndrome appears to be congenital in our cases. Congenital hemihypertrophy is more frequent in males and involves the right side more often than the left (Ringrose *et al.*, 1965), whereas in our patients the left side was involved and all 3 were female (Table 1). The congenital form is usually idiopathic, but may be associated with a number of intra-abdominal neoplasms (Pfister *et al.*, 1975), such as Wilms' tumour (Miller *et al.*, 1964; Fraumeni *et al.*, 1967) and neuroblastoma (Lewis and Geschickter, 1934). Adrenocortical tumour and hepatoblastoma (Ishak and Glunz, 1967; Geiser *et al.*, 1970) have frequently been reported. Occasionally the hemihypertrophy is recognized after removal of these neoplasms (Boxer and Smith, 1970). Patients with medullary sponge kidneys (Harrison and Williams, 1971; Eisenberg and Pfister, 1972; Sprayregen *et al.*, 1973) and neurofibromatosis (Huse, 1944; Ishak and Glunz, 1967; Praharaj *et al.*, 1969; Haicken, 1970) have also been described with hemihypertrophy. Neoplasms or evidence of phakomatosis were not seen in our patients. Vascular or lymphatic malformations give rise to a limited form of hypertrophy involving limbs or parts of limbs, but there was no evidence to suggest the presence of such defects in our patients.

TABLE 1. CLINICAL ASPECTS OF THE HEMI 3 SYNDROME

	Case 1	*Case 2*	*Case 3*
Onset	Congenital	Congenital	Congenital
Course	Static	Static	Static
Side/involvement	Left	Left	Left upper quadrant
Handedness	Right	Right	Right
Family history	+	+	+
Meningomyelocoele	−	−	+
Progressive scoliosis	+	+	+
Widening of long bones	+	+	+
Shortening of affected limbs	+	+	+

In the cases presented here the affected limbs were shorter and thicker as compared with the normal side, both clinically and radiologically. In patients with hemihypertrophy the limbs are usually equal in length, but cases have been reported with shortening of the affected and enlarged member (Keipert, 1973).

The neurological abnormalities associated with hemihypertrophy have been poorly documented. Mental retardation is said to occur in 15 to 20 per cent of cases (Gesell, 1921; Morris and MacGillivray, 1955). Our patients were of normal intelligence. Neuropathological examination of the brain in patients with congenital hemihypertrophy has been reported as normal, but a large ipsilateral hemisphere has occasionally been described (Schenkein *et al.*, 1974). Radiologically, asymmetry of the skull is frequently found in congenital hemihypertrophy, but skull x-rays were normal in the present group of patients. CT scans and pneumoencephalography in 2 of our patients did not reveal abnormality or asymmetry (Table 3). EEGs were also normal, supporting the hypothesis that this is not a cerebral cortical or hemisphere disease, and distinguishing it from hemiatrophy of cerebral origin.

TABLE 2. NEUROLOGICAL ABNORMALITIES SEEN IN PATIENTS WITH THE HEMI 3 SYNDROME

	Case 1	*Case 2*	*Case 3*
Hypertrophy	L. hemi	L. hemi	L. upper quadrant
Power	↑	↑	↑
Tendon reflexes	R↑? L↓	R↓ L↓	R↑ L↑
Plantar responses	O	O	O
Pain and temperature	↓	↓	↓
Other sensory modalities	N	N	N
Sweating	N	N	↓
Pupil	N	N	↓

TABLE 3. LABORATORY INVESTIGATIONS

	Case 1	*Case 2*	*Case 3*
Blood chemistry	N	N	N
Skull x-ray	N	N	N
Myelogram	N	N	Spina bifida L3–S2, rachischisis
CSF protein and cells	N	N	N
PEG	N	—	—
CT scan	—	N	—
Karyotype blood	N	N	N
Karyotype skin	N	—	N
Nerve conduction studies	N	N	N
EMG	N	N	N

Unilateral loss of pain and temperature sensation is an unusual finding in association with hemihypertrophy. In addition, one of our patients (Case 3) had decreased sweating in her affected upper quadrant (Table 2). Wiseberg (1931) described a 22-month-old child with decreased sweating of the hypertrophic side. Mayers (1926) reported a female patient with hemihypertrophy and exaggerated heat and cold sensation on the opposite side. It is possible, and in light of our experience very likely, that this child had decreased sensation on the enlarged side. Fox and Huott (1974) described a woman with long-standing enlargement and decreased pain and temperature sensation on the left side, and areflexia of the left upper limb. This patient, however, had increased reflexes in the left lower limb, strength of the enlarged side was apparently not increased, and scoliosis was not a clinical feature. Wiseberg's patient may have had the syndrome described here; very likely Mayer's case did, and the woman described by Fox and Huott seems to have had the same disorder, despite certain clinical differences. More recently increased skin temperature has been documented by thermography in a patient with congenital hemihypertrophy, confirming evidence for autonomic abnormalities in this disorder (Furukawa and Shinohara, 1981).

Scoliosis, clubfoot, spina bifida, and various skeletal abnormalities, including polydactyly and syndactyly, have been described in association with congenital hemihypertrophy (Wakefield and Hines, 1933; Ward and Lerner, 1947; Bryan *et al.*, 1958). In 2 of our cases the scoliosis was the presenting feature, but the neurological abnormalities provided clues to the recognition of the underlying syndrome. All 3 patients had a thoracic scoliosis convex to the left, the side of their hemihypertrophy. They had compensatory lumbar scoliosis, none had detectable bony abnormalities at the level of the hemihypertrophy but the third patient had spina bifida at the level of her meningocoele. The scoliosis corresponded to the idiopathic form, but it was unusual in being left convex in these 3 females; at this age the right convex form usually predominates. It was probably related to the asymmetry in growth, bulk, power and sensation but its precise mechanism is unclear. The severity of the scoliosis was such that it required surgical correction in all 3 patients, resulting in stabilization for periods of up to nine years.

Loss of pain and temperature sensation is commonly seen in syringomyelia and tumours of the spinal cord. There are a number of observations which suggest that the hemi 3 syndrome may be unlike a syrinx. Syringomyelia tends to be a chronic stepwise or slowly progressive disorder with lower motor neuron changes manifested by weakness and atrophy, and accompanying neurogenic changes on electromyography. Power is decreased or normal, although it has been stated that the loss of pain sense may allow excessive traction on tendons and other pain-sensitive structures during active muscular contraction. Muscular enlargement or hemihypertrophy with shortening of the affected limbs has not been reported. In association with syringomyelia, scoliosis and spinal closure defects are frequent, and this diagnosis was strongly entertained in each of our patients. Myelography was performed in all 3 and axial tomography of the spine in 1; there was no evidence for a syrinx. Thus the clinical presentation, course, and investigations did not provide support for such a diagnosis.

A number of theories have been proposed to explain the pathogenesis of hemihypertrophy. These include abnormal cleavage of the early blastomeres and more specific irregularities of maturation and differentiation of morphogenetically determined structural primordia (Gesell, 1927; Noé and Berman, 1962). Although occasional familial cases of hemihypertrophy have been described (Reed, 1925; Scott, 1935), this has been the exception rather than the rule. None of our patients had a positive family history of hemihypertrophy. Most cytogenetic studies for mosaicism and altered chromosomes have been negative (Duven, 1973), although triploidy has been noted (Ellis *et al.*, 1963; Ferrier *et al.*, 1964). In our patients, chromosomal abnormalities were not found.

Patients with the hemi 3 syndrome appear to have a static unilateral longitudinal congenital lesion which is extensive in distribution. There is evidence to suggest that this may be part of the spectrum of closure defects of the neural tube. In our series, one patient had a meningomyelocoele and another had a sister with a similar spinal defect. The family pedigrees demonstrated several abnormalities ranging from anencephaly, the most severe form of closure defect, to mild scoliosis and spina bifida occulta. Furthermore, all three families showed an excessive number of other congenital malformations in their pedigrees. This would suggest that, in these families, there is an increased genetic predisposition, not only to neural tube defects, but also to malformations of other systems. Since congenital malformations are known to be inherited in a multifactorial fashion (Carter, 1965), with interactions of polygenes and the environment, it may be postulated that these malformations may have some of their genetic susceptibility or liability in common.

This study suggests the presence of an abnormality of longitudinal closure or development of the nervous system in our patients and in their families. The prevalence of neural tube closure defects in the families of our 3 patients is quite comparable to that found in families of probands with meningomyelocoele or anencephaly, and thus these conditions would appear to be aetiologically related. Based on genetic and epidemiological evidence, an aetiological relationship to spina bifida cystica and anencephaly has also been demonstrated for spina bifida occulta with multiple neural arch involvement or with a large defect of one arch (Laurence *et al.*, 1971; Gardner *et al.*, 1974), congenital scoliosis associated with multiple vertebral anomalies (Wynne-Davies, 1975), and for spinal dysraphism (Carter *et al.*, 1976).

In families of probands with spinal dysraphism or multiple vertebral anomalies who do not themselves have classical neural tube defects, the risk of spina bifida or anencephaly in siblings is 3 to 5 per cent (Wynne-Davies, 1975; Carter *et al.*, 1976). This is similar to the risk of classical neural tube malformations in siblings of probands with spina bifida cystica or anencephaly (Carter *et al.*, 1968; Carter and Evans, 1973; Lippman-Hand *et al.*, 1978). This risk has been shown to increase with the number of siblings affected (Carter and Roberts, 1967), a finding which is compatible with multifactorial inheritance of these malformations (Carter *et al.*, 1968). One United States study, however (Holmes *et al.*, 1976), emphasized the aetiological heterogeneity of neural tube defects, and found the precurrence (i.e. the occurrence of abnormalities in siblings born before the proband) and recurrence rates for isolated anencephaly, meningomyelocoele, meningocoele and encephalocoele to be only 1.7 per cent and 0 per cent, respectively, after single gene disorders and chromosomal defects had been excluded. These differences may be explained at least in part by geographic variation in the incidence of neural tube defects (Carter *et al.*, 1976; Lippman-Hand *et al.*, 1978), and by the small numbers in this study.

It would thus appear that the syndrome of hemihypertrophy, hemihypaesthesia, hemiareflexia and scoliosis forms part of a spectrum of genetically and embryologically related CNS malformations with multifactorial inheritance. Just as with anencephaly, spina bifida cystica, spinal dysraphism, congenital scoliosis associated with multiple vertebral anomalies, and spina bifida occulta involving multiple neural arches, patients with this form of hemihypertrophy, their siblings, parents and their parents' siblings should be offered genetic counselling and prenatal screening for neural tube malformations.

Unilateral loss of pain and temperature sensation is common in syringomyelia and generalized loss of pain and temperature sensation has been described in other congenital disorders. In the Riley Day syndrome (familial dysautonomia) there is a decreased number of small myelinated nerve fibres as well as loss of unmyelinated axons on peripheral nerve biopsy (Aguayo *et al.*, 1971). It was postulated that this sensory abnormality is associated with developmental arrest of the small neuronal population of the dorsal root and autonomic peripheral ganglia. Pathological studies in a patient with hereditary sensory neuropathy with anhidrosis and selective pain and temperature sensory loss demonstrated a striking absence of the small neuronal population of the dorsal root ganglia, hypoplasia of the root entry zone, and absence of Lissauer's tract and the substantia gelatinosa (Swanson *et al.*, 1965).

There were no abnormalities of the motor neurons, and the spinothalamic tracts appeared to be normal. Interestingly, dural clefts with fibrosis were noted along the spinal cord which could suggest a remote cord lesion, perhaps a closure defect. Goebel *et al.* (1980) confirmed a virtual absence of unmyelinated axons in peripheral nerve.

Isolated loss of pain and temperature sensation may result from lack of development or abnormal development of the small neuron population of the dorsal root ganglia or their central connections. These cells are derived from migrating truncal neural crest cells. The neuroblasts forming the dorsal root ganglia in the chick embryo result from two populations of cells: the early neurons develop sensory modalities for touch and proprioception, whereas the later developing neurons subdivide into small neurons subserving pain and temperature modalities and large neurons concerned with proprioceptive Ia afferents (Hamburger and Levi-Montalcini, 1949). It appears that the small neurons which probably represent the medial dorsal cells of the developing dorsal root ganglion are under the influence of nerve growth factor (Weiss, 1970). Nerve growth factor does not appear experimentally to prevent migration or mitosis of the medial dorsal neuroblasts, but these cells will degenerate in excess numbers without nerve growth factor being present. This entire subject has recently been reviewed (Mobley *et al.*, 1977*a*, *b*, *c*). Interestingly, elevation of nerve growth factor has been reported in the serum of patients with the Riley Day syndrome, but its significance is not well understood (Schenkein *et al.*, 1974; Siggers *et al.*, 1976). More recently reduced nerve growth factor has been observed in the skin fibroblasts of patients with familial dysautonomia (Schwartz and Breakefield, 1980). Increased serum activity of nerve growth factor fractions have now been measured in the serum of patients with peripheral von Recklinghausen's disease (Fabricant and Todaro, 1981). These findings suggest that nerve growth factor or a similar substance may play a role in the genesis of these disorders. Hökfelt *et al.* (1976) have found substance P-like activity and somatostatin-like activity in different cells in the small neuron cell population of the dorsal root ganglia in rats. The role of these neuropeptides at that level is unclear, but substance P may modulate pain perception and this function may be lost if those neurons are not present.

As previously noted, the 'idiopathic' form of hemihypertrophy has been associated with neurofibromatosis, phaeochromocytoma and neuroblastoma, as well as with other abnormalities. These disease entities all appear to arise from the neural crest cell or its derivatives and their interrelationships have been described under the broad concept of 'neurocristopathies' (Bolande, 1974; Tischler *et al.*, 1977). Hemihypertrophy is likely to be one of the teratogenic abnormalities of the neural crest cells. Our patients gave evidence of an extensive longitudinal defect, and all 3 families had significant abnormalities of neural tube closure. Those cells destined to form the neural crest cells are closely related to development and closure of the neural tube. Abnormalities of closure may also affect the multiplication and migration of neural crest cells, resulting in a clinical picture of abnormal pain and temperature sensation as well as spinal closure defects. The aetiology and pathogenesis of this syndrome remain speculative. Biopsy of the dorsal root ganglia and pathological studies may help elucidate the problem further.

It is important to recognize the hemi 3 syndrome and to consider it in all patients with hemihypertrophy and in those who are presumed to have hemiatrophy or idiopathic scoliosis. A thorough search for syringomyelia is still necessary. There is no progression of the neurological deficit, but the scoliosis appears progressive and requires surgical stabilization.

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SENSORY CONSEQUENCES OF COMMISSURAL MYELOTOMY*

A CHALLENGE TO TRADITIONAL ANATOMICAL CONCEPTS

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SUMMARY

Twenty-five cases of commissural myelotomy were studied. Representative cases are reported, including a histological examination of the lesion in one. Although the purpose of the operation is to produce a cuirass of loss of pain sensibility by dividing the spinothalamic and spinoreticulothalamic fibres as they decussate in the anterior commissure of the cord, this result is not always obtained. Whether or not the expected sensory loss is obtained, the chronic pain for which the operation is performed can be relieved. Sensibility tends to return towards normal after myelotomy. Even with substantial recovery of sensory loss, the pain for which the operation was performed can remain absent. Asymmetrical sensory loss may be produced by the operation; reasons for this are suggested. Differences between the results of commissural myelotomy and anterolateral cordotomy are discussed.

Unlike the results of anterolateral cordotomy, which can be accounted for on the basis of known anatomy, the results of commissural myelotomy are inexplicable on present anatomical knowledge. Attention is drawn to the results of myelotomy reported originally by Hitchcock and confirmed by other neurosurgeons in which a short myelotomy incision in the upper cervical cord caused loss of pain over a vast region of the body. The difficulty in explaining the patterns of sensory loss in these cases is discussed. The literature on pathways alternative to the spinothalamic and spinoreticulothalamic is reviewed. It is argued that the central incision cannot cause relief of pain merely by cutting an afferent pathway, and it is suggested that this lesion blocks impulses entering into, in, or leaving the spinothalamic complex. The accurate localization of pinprick and thermal stimuli *via* the spinothalamic tract is demonstrated.

INTRODUCTION

The original concept of the operation of commissural myelotomy was to divide the crossing fibres of the spinothalamic tracts. J. G. Greenfield, who suggested the operation to Armour (1927), and also Putnam (1934) and Leriche (1936), who each conceived the operation independently, expected that the results would be like those of a bilateral anterolateral cordotomy over a cuirass area of the body; within this area they expected to produce an absence of pain and thermal sensibility. This result is sometimes but not always obtained. What is most surprising is that the pain for which the operation is performed may be relieved without there being any cutaneous sensory loss on testing. Another unexpected feature of the operation is that when sensory loss does occur, it extends further caudally than would have been expected. It is also remarkable how a short midline incision in the cord may produce a large craniocaudal extent of loss or diminution of pain and thermal sensibility. When sensory loss occurs, it passes off more quickly than after anterolateral cordotomy. Yet, unlike cordotomy, if sensibility returns to normal, the chronic pain may not return at the same time.

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A theoretical advantage of myelotomy is that spinothalamic fibres from both sides of the body are divided and therefore bilateral and midline pain can be relieved. To treat such pain by bilateral anterolateral cordotomy is liable to upset the control of micturition and defaecation, it can upset vasomotor control, and it may cause weakness of the lower limbs. A unilateral cordotomy performed in the cervical cord may interfere with respiration. These unwanted effects do not occur with a myelotomy. On the other hand, the relief of pain usually lasts less long than that achieved by anterolateral cordotomy, often not more than a year. In myelotomy, some damage is also done to fibres other than those concerned with conduction of nociceptive impulses. The posterior columns have to be separated over the length of the incision and may be damaged. (The effects of this damage will be reported in a subsequent paper.) The incision also divides decussating spinocerebellar and corticospinal tract fibres. Damage to the grey matter may not be confined to the central zone and it may be more extensive than intended. In this paper, we discuss the effects of the operation on the relief of pain, the nature of the sensory loss, and the problems involved in accounting for the findings on the basis of classical anatomy.

The fact that pain can be relieved without there being any obvious sensory loss raises the question as to whether the relief of pain is actually due to cutting the crossing fibres of the spinothalamic and spinoreticulothalamic tracts, as the operation was conceived to do. We will therefore consider other available afferent pathways in the cord than this spinothalamic complex of fibres. The term spinothalamic complex will be used to denote spinothalamic and spinoreticulothalamic tracts. Evidence will also be presented to show that noxious and thermal stimuli are accurately localized in the parts of the body deprived of posterior column fibres.

CASES

Twenty-five cases of myelotomy have been studied; 5 are presented here as they are of particular interest; in one of these there was histological examination of the lesion.

Case 1. Female, Aged 53 Years

The first case had a post-mortem examination of the spinal cord so that the myelotomy lesion was studied. This patient is also important as there was no detectable sensory loss on testing and yet the pain was relieved.

The patient had a radical mastectomy for carcinoma of the breast, spreading to the lymph nodes in the breast and axilla. Two years later, spinal metastases were found causing severe pain in the lower back and lower limbs. A transphenoidal hypophysectomy gave immediate relief of pain but this was short-lived. The pain returned and further bony metastases were found in the thoracic and lumbar vertebrae. The pain in the left lower limb was intense, and because of weakness of this limb, she could hardly walk.

Six months later a commissural myelotomy was performed, extending from the eighth thoracic to the first lumbar vertebrae. The pain was relieved, but gradually returned. It must be emphasized that even during the time of maximal pain relief, there never was any detectable loss to pain of pinprick. Apart from these observations, later sensory examination was not undertaken owing to the severe illness of the patient. After the operation, she could not walk, even with a brace. She died 185 days after the myelotomy.

Histological examination of the spinal cord. Sections from the level of the operation in the lower thoracic segments show the location of the myelotomy incision (fig. 1A–C). The track of the lesion passes through the posterior columns into the central grey matter. The cord is almost divided in two in some sections (fig. 1B). There is degeneration in the posterior columns resulting from the surgical lesion, shown by pallor of myelin staining. The lesion was somewhat oblique and off centre, as the degeneration is greater in the left posterior column and, on the left, the track of the lesion passes through the neck of the posterior horn close to the caput, continuing anteriorly into the left anterior horn. There is extensive necrosis and cavitation in both anterior horns and in the central grey matter (fig. 1A–C). There is almost complete loss of nerve fibres in the grey matter, only a very few being present

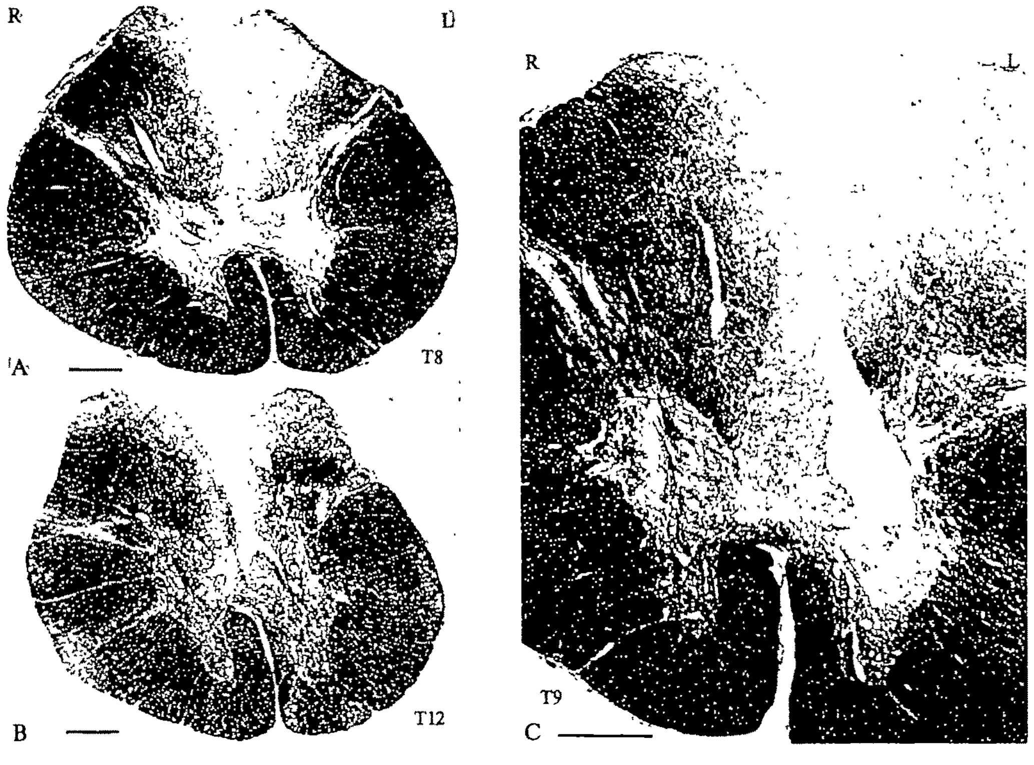

FIG. 1A–C. *Case 1.* Sections, stained to show myelin, from the lower thoracic segments of the spinal cord showing location of myelotomy lesion and consequent degeneration and necrosis. Pallor indicates degeneration. A and C, Weil preparations; B, Loyez and neutral red preparation. Bar = 1 mm.

(fig. 1C) close to the anterior median fissure; these appear to be coming from or going to the anterior horns. There is degeneration in the lateral white columns on both sides (fig. 1A and B) due to destruction of neurons and fibres in the grey matter. This degeneration is most marked on the periphery at about the level of the equatorial plane of the cord and in the deeper white matter, where it is more scattered. The peripheral degeneration is in the spinocerebellar system; there is also scattered, less intense degeneration between the periphery and the grey matter, part of which consists of degenerating fibres of the spinothalamic complex.

Ascending degeneration is consistent with the findings in the lower thoracic cord. In the first thoracic segment, which was the most cranial segment available for examination, pallor, indicating degeneration, is present in the anterolateral and lateral columns; this is in the distribution of the posterior and anterior spinocerebellar tracts. Some fibres of the spinothalamic complex are likely to be present within the medial part of the latter tract, but they could not be positively identified. The length of survival after the operation was too long to permit the use of histological methods showing degenerating axons, which would have given more information as to which tracts were involved.

Comment. The histological preparations of the cord show that the incision between the eighth thoracic and first lumbar segments has divided decussating spinothalamic fibres; yet it did not cause any loss of pain and thermal sensibility on testing. The operation nevertheless relieved most of the pain in the patient's lower back and lower limbs.

Case 2. Male, Aged 69 Years

The second case presented is valuable on account of extensive clinical investigation over a period of three years. The patient cooperated in the repeated examinations, and he hoped, as we did, that they would be correlated with the results of post-mortem examination. Despite all prior arrangements, we were not informed when he died and so no post-mortem was obtained. He showed the greatest degree of sensory changes of any of the cases in our series, and it must be presumed that the damage to the cord was more extensive than in other cases. The extent of the initial lesion may have become larger owing to vascular involvement.

The patient had had pain associated with carcinoma of the lower end of the oesophagus. There was central and bilateral deep aching pain between the scapulae. On two occasions infiltration of the muscles of the back with local anaesthetic removed all the pain for 15 min and reduced it for 2 h. We concluded that the pain was coming mainly or entirely from the muscles of the back rather than from the oesophagus itself. The relevant segments were estimated to be the fourth to the seventh thoracic. Before the operation, tactile sensibility examined with von Frey hairs was normal. Pinprick was tested quantitatively, in that weighted pins were used and the number of spots in marked out areas of 1 cm^2 on which a pin was felt as painful was scored. Before operation, the lightest pinpricks were felt as painful at more than 20 points per cm^2 in any part of the body.

The operation was performed by Sir Wylie McKissock, before the introduction of the operating microscope. The laminectomy extended from the fourth to the seventh thoracic vertebrae. A needle was inserted to a depth of 5 mm and a lesion was made, extending 1 cm cranial and 1 cm caudal to the laminectomy opening, the total length being about 65 mm. This lesion was planned to divide decussating fibres of the spinothalamic complex from the fourth to the ninth thoracic segments.

The operation produced a cuirass of sensory loss, as was expected, and it gave some relief from the pain; but this relief lasted less than four weeks. Examination on three occasions 24 to 60 h after the operation showed a loss to the pain of heavy pinprick: a pin of 140 g weight was not felt on chest, abdomen and back. When it was applied repetitively, instead of summating to a constant burning pain, it was felt as repeated tapping. This region is shown in fig. 2. The loss of pain sensibility did not extend quite as far caudally on the left as on the right and the borders were less definite and clear-cut than after

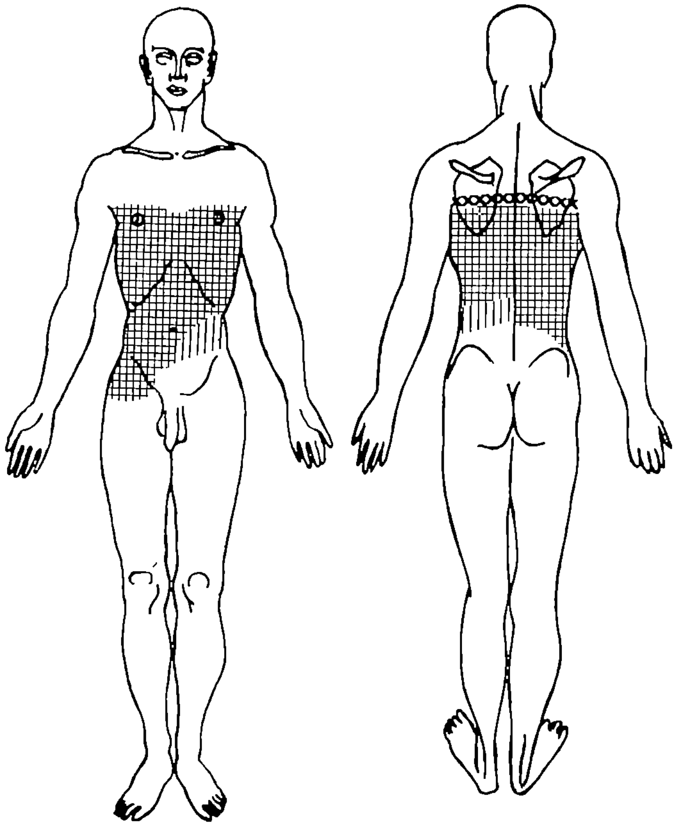

FIG. 2. *Case 2.* Sensory findings within two days of operation. Cross-hatching shows region in which repeated hard pinprick and pinprick of 140 g were not felt as painful. Hatching shows region where light pinprick was not felt as painful. Crosses show region covered by dressings and not examined.

anterolateral cordotomy. Throughout this cuirass, all touches with cotton wool felt less firm than in the normal region cranial to the operation.

During the first ten days, the area of insensitivity to deep pain—as tested with the pressure algometer—largely corresponded with the region of loss of cutaneous pain, but extended further caudally, as shown in fig. 3. There was a small region on the left lower thigh where pressure was painless; and pressure could be applied without pain over most of the *os innominatum*, particularly along the sides of the body. The injection of 6 per cent saline into both quadriceps muscles caused no pain.

Evidence concerning visceral pain was obtained from squeezing the testes and by the incidental occurrence of cystitis. There was no loss of pain on squeezing either testis. There was guarding and tenderness on pressure over the bladder and pain from the cystitis. The sensory input from the testes, according to Bors (1950), reaches the cord caudal to the ninth thoracic segment, and that from the bladder in the second, third and fourth sacral nerves. It is apparent that pain from visceral structures from the tenth thoracic segments caudally was being felt.

It was deduced that the cranial level of division of decussating fibres of the spinothalamic tract involved fibres of the fifth thoracic segment. For cutaneous sensibility, the caudal level indicated asymmetrical division of fibres from the two sides. Loss of deep pain extended further caudally than loss of cutaneous pain, extending into the lumbar segments. No evidence of loss of visceral pain was found; structures caudal to the tenth thoracic segments gave pain on stimulation.

Early after the operation, a radiant heat stimulus was not felt in the region in which pinprick sensibility was absent. Three to four weeks after the operation, water at 60° C caused a slight sensation of warmth on the left side and no thermal sensation on the right. This form of sensibility soon recovered further, so that it felt 'quite warm' on the left and 'slightly warm' on the right. Ethyl chloride spray and ice always caused some thermal sensation. On the left, they felt cold; on the right, they caused a sensation first of warmth and then of slight cold. Nowhere on the trunk, chest or abdominal wall did they feel very cold, but they felt normally cold on the lower limbs. For thermal sensibility, therefore, there was asymmetry between the two sides. The caudal boundary was always rather indefinite on the left, varying between the eighth thoracic and first lumbar segments; on the right it extended to the second lumbar segment. Thus at first, thermal sensibility was affected similarly, but not as severely, as that of pain of pinprick. But it recovered more quickly than pinprick, and did so asymmetrically.

By two months after the operation, there had been further recovery of pain of pinprick and there was a difference between the back and abdominal wall on the left. On the left side of the abdomen, pinprick of 60 g was not felt as painful but was reported as touch, although at many places on the left side of the trunk and the back, this pinprick was painful. Everywhere on the right side, this stimulus was felt only as touch. In the places where pinprick was felt as painful, it was correctly localized, but where it was felt only as touch, it was often mislocalized by 10 cm. The painful stimulus of water in a tube at 85° C was felt everywhere as a burning pain.

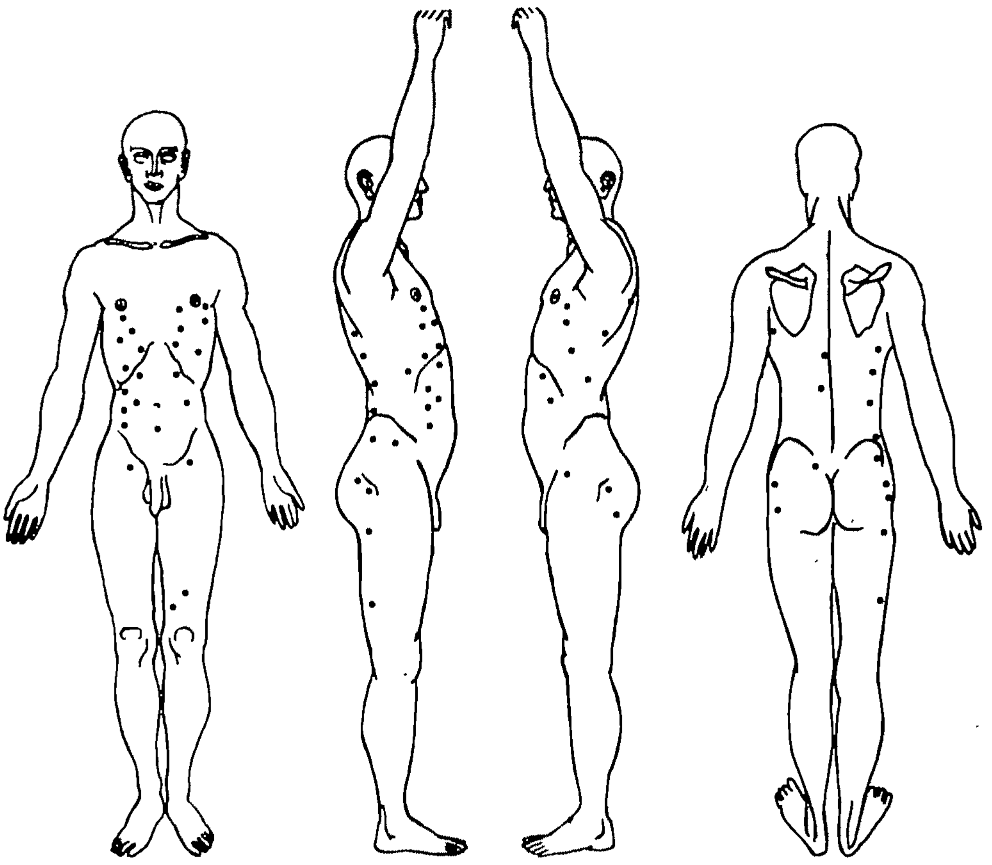

FIG. 3. *Case 2.* Ten days after operation. Dots show region in which deep pain could not be induced by algometer at pressure of 40 lb.

Two years after the operation pain of pinprick was only very slightly diminished throughout the region which had been analgesic to pinprick immediately after the operation. Deep pain was still diminished along the costal margins, the upper abdominal wall, the centre of the back and the sides of both thighs. The cold stimulus of ethyl chloride showed a just detectable difference within the original region of diminution of this sensation, slightly more marked on the right.

Two and a half years after the operation, deep pain sensibility was still diminished in the centre of the back, extending around the right side. There was a raised threshold over the lower thoracic cage and the upper abdominal wall. For pinprick, the boundaries of loss of sensibility immediately after the operation were still detectable on the right and at the cranial boundary on the left; the caudal boundary on the left had extended further caudally onto the front of the thigh. Not only had this region become more extensive but on both sides there was more loss to pinprick than there had been earlier. Water at 45° C felt warm though not hot in the original area of diminution of thermal sensibility; and the patient could just detect a diminution in cold sensation in the same region.

Throughout the postoperative period, proprioception was severely impaired in both lower limbs. He had at first no knowledge of passive movement of his feet or toes. He was severely ataxic, and if he walked with his eyes shut, he fell. These defects improved with time. From the fourth thoracic segment caudally tactile sensibility was much reduced. Although stroking with cotton wool was felt between the fourth and eighth thoracic segments bilaterally, the quality of the sensation was abnormal in that it felt heavier and the patient did not know what the stimulus was; but localization and direction of the stroking were correct. Tactile sensibility was also diminished between the eleventh thoracic and second sacral segments on the right and the twelfth thoracic and fourth sacral segments on the left, but stimuli were felt more clearly than over the thoracic cage. The stronger stimulus of stroking with a finger was felt on the trunk and thoracic cage. Further caudally this tactile stimulus sometimes evoked no sensation. He had little awareness of his feet being touched and sometimes localized a stimulus on the wrong foot. Often he felt the stimulus but was unable to localize it.

Comment. An incision intending to divide crossing fibres of the spinothalamic complex from the fourth to the ninth thoracic segments in fact divided fibres subserving cutaneous pain and temperature from the fifth to the eleventh thoracic segments on the left and those from the fifth thoracic to the second lumbar segments on the right. The level of loss of these sensory modalities extended bilaterally to the cranial limit of the incision into the cord. This indicates that some fibres of the spinothalamic complex originate and cross within the same segment as that entered by the related posterior root. The loss of deep pain extended considerably further caudally than that of cutaneous pain sensibility. It included both quadriceps and the lumbar regions of the *os innominatum*. It therefore included the third or fourth lumbar segments. For visceral pain, the loss did not include the testes, supplied by nerves caudal to the tenth thoracic segments, nor the bladder, supplied by sacral nerves.

It is important to note that there was severe ataxia and loss of proprioception from the lower limbs. Below the fourth thoracic segment bilaterally down to the level of the umbilicus, there was some tactile loss which is attributed to division of spinothalamic fibres: for from this region there was loss or diminution of all forms of spinothalamic sensibility. The caudal extent of division of fibres of the spinothalamic complex cannot be deduced, as the levels for cutaneous and deep loss of pain sensibility were different; however, there is no evidence of spinothalamic fibres caudal to the fourth lumbar segment being involved. Caudal to these segments the loss of tactile sensibility, together with great disruption of proprioception and the presence of ataxia, is attributed to damage to the posterior column fibres involved in the operative incision. In this most caudal region from which spinothalamic fibres were apparently intact and posterior columns affected, pinprick, pressure pain, warm and cold stimuli were accurately localized. It is concluded that in the region of the body supplied only by fibres of the spinothalamic complex and deprived of fibres of the posterior columns, painful and thermal stimuli are accurately localized.

There was an intermediate region of the body in which touch was not felt and light pinprick was often not felt. It was deduced that fibres of both spinothalamic and posterior column systems supplying this region had been divided. This region on the body fluctuated in location and actually seemed to extend a segment or two further caudally over the years. On the right the affected spinal segments appeared to be the twelfth thoracic and first lumbar and on the left the eleventh thoracic to the second lumbar inclusive.

Aspects of this case requiring emphasis are the following: (1) the long craniocaudal extent of diminution in pain sensibility for skin and deep tissues caused by the short myelotomy incision; (2) the fact that loss of pain and thermal sensibility came right up to the cranial limit of the lesion; (3) the manner in which recovery of sensibility occurred, being first on the back and one side, leaving the front of the body still affected; (4) the difference in the caudal levels of loss of deep pain sensibility and superficial pain; and (5) the ability to localize noxious and thermal stimuli in a region with many posterior column fibres absent and spinothalamic fibres present.

The following cases are presented briefly as they illustrate the distribution and kind of sensory loss which is characteristic of myelotomy and also the extensive area affected by the short incision.

Case 3. Male, Aged 52 Years

This patient suffered from very severe bilateral deep midline pain due to carcinoma of the oesophagus, invading the mediastinum. A commissural myelotomy was performed which removed almost all his pain and he returned home. He lived for fourteen weeks after the myelotomy, having had no return of severe pain. The vertebral level for the operation was from the first to the fourth thoracic; the cord level was presumed to be from the second to the fifth thoracic segments; the incision was 40 mm long. The region of diminution in sensibility is shown in fig. 4. The upper border on the left involved the seventh cervical segment, and on the right, the fourth thoracic. The caudal border was at the tenth thoracic on the left and the eighth thoracic segment on the right.

Comment. A feature of this case was the large extent of diminished pain sensibility with a short myelotomy incision. It appears from the asymmetry of the sensory changes that the incision did not remain in the midline throughout its length; it may have deviated in a similar way to that shown in Case 1, fig. 1.

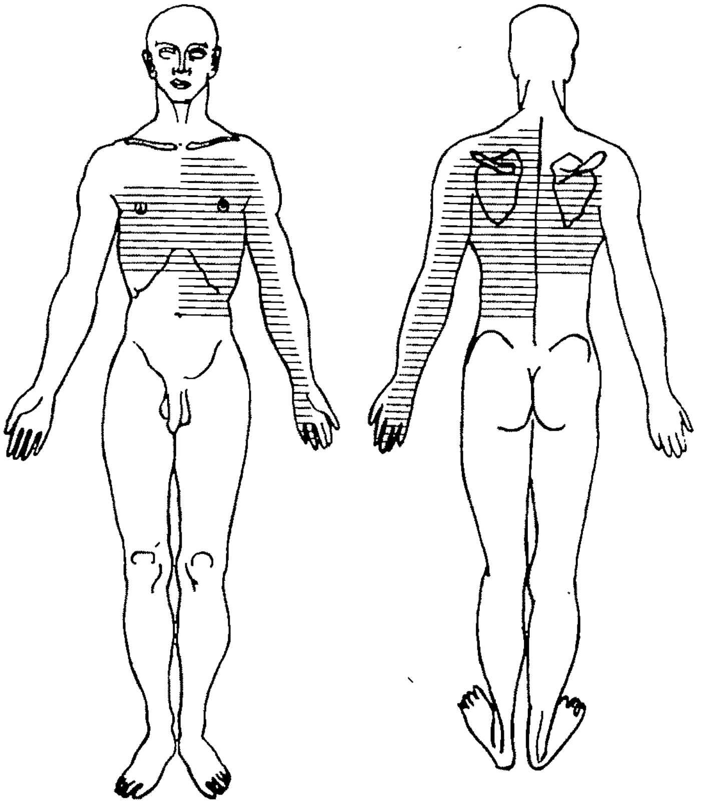

FIG. 4. *Case 3.* Two weeks after operation. Hatching shows area in which heavy pinprick caused only slight pain.

Case 4. Male, Aged 64 Years

This patient was suffering from abdominal pain due to carcinoma of the colon with metastases throughout the peritoneum. His pain was so severe that he could not get onto the examination couch. He remained in a semiflexed position as extending his spine was very painful. The pain was also severe in the right groin and thigh, reaching as far as the knee. A commissural myelotomy was performed at the level of the sixth to ninth thoracic vertebrae; the cord level was presumed to be from the eighth to the eleventh thoracic segments; the incision was 50 mm long. The pain relief was striking. The patient got out of bed and walked within 48 h of the operation. He was able to go home, and lived a further six months. He remained quite comfortable, despite 'some soreness' in his abdomen.

The operation produced a great decrease in pain sensibility in a cuirass distribution. On the first day after the operation, the upper boundary of this region was between the nipples and the xiphisternum anteriorly; it passed horizontally around the chest wall. This is considered to be at the eighth thoracic segment, the upper segmental level of the incision. By the third day, the upper level had changed, and is shown in fig. 5. This level may be regarded as the tenth to the eleventh thoracic segments on the left and the ninth thoracic segment on the right anteriorly. It passed around the trunk on both sides to meet at the spine of the fifth lumbar vertebra. The lower level showed a tongue-like extension on the front of the thighs, with the point of the tongue more lateral than the midline of the limb. Touch was felt normally everywhere.

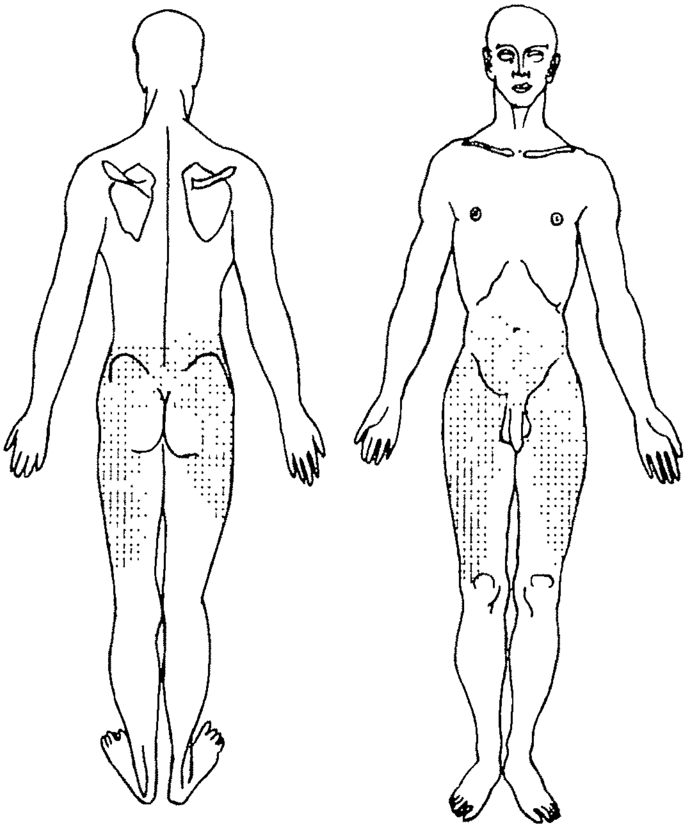

FIG. 5. *Case 4*. Cross-hatching shows region in which weighted pinprick caused only slight pain.

Comment. This patient showed a cuirass of sensory loss with the cranial border running horizontally round the trunk and the caudal border forming tongue-like extensions on the lateral and posterior aspects of the thighs.

Case 5. Female, Aged 58 Years

This patient had a carcinoma of the cervix invading the left lumbosacral plexus, causing very severe pain in the left lower limb. She had foot-drop and diminution in all forms of sensibility in the fifth lumbar and first sacral segments. A commissural myelotomy was carried out from the eighth to the eleventh thoracic vertebrae; this probably would be at the segmental level of the ninth thoracic to the first lumbar. The sensory loss due to the operation was insufficiently caudal to cover the region of the pain. The region of decreased pain of pinprick two weeks after the operation is shown in fig. 6. Anteriorly, the level was just below the costal margins; it passed horizontally around the sides; near the midline at the back, it dipped down to the spine of the fifth lumbar vertebra. This level would be considered to be cranial to the ninth thoracic segment anteriorly; the caudal level was in the midthigh, sparing the adductor surface. This would correspond roughly with the second to third lumbar segments.

Comment. The cuirass of sensory loss obtained was insufficiently caudal to relieve the pain. However, the total extent of sensory loss was larger than would

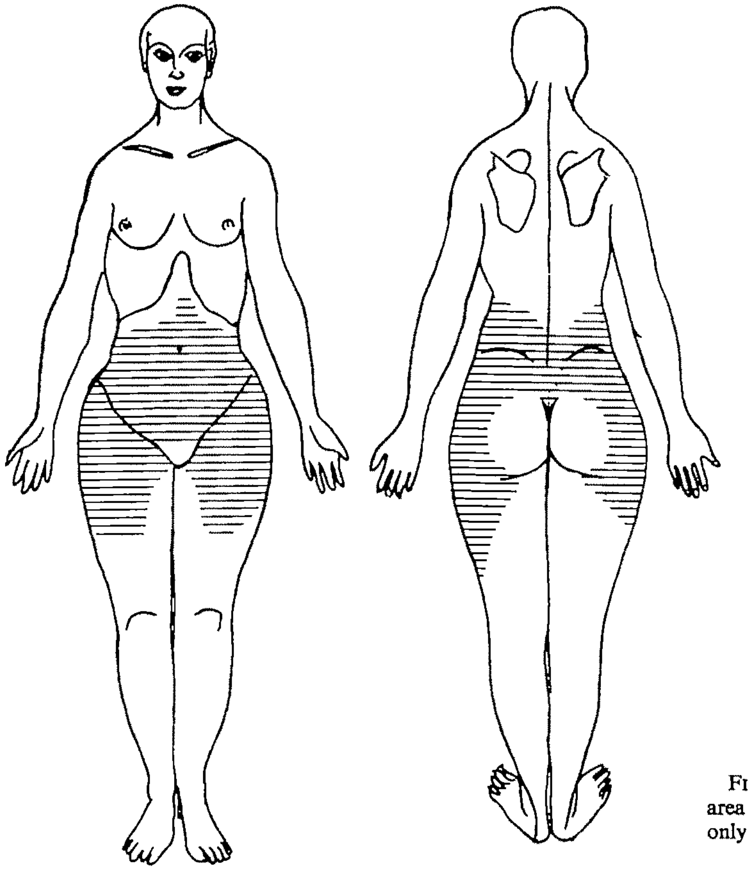

FIG. 6. *Case 5.* Hatching shows area in which heavy pinprick caused only slight pain.

have been expected from the length of the incision in the cord. The boundary passed around the trunk at right angles to the long axis, sinking in the midline at the back.

DISCUSSION

Commissural Myelotomy and Afferent Pathways in the Spinal Cord

The French surgeons who were the first to make extensive use of myelotomy soon found that the operation had different sensory effects from those resulting from a limited bilateral cordotomy. In 1944, Mansuy and coworkers reported that sometimes the removal of the pain was not immediate but that it took a few days to occur. They wrote 'Contrary to what one expects, myelotomy causes only very little disturbance' in sensibility. 'Painful and thermal sensibility is modified in about 30 per cent of cases; these are slight effects that one has to search for carefully.' They never obtained a cuirass of total analgesia in the relevant region. The largest series of myelotomies is that reported by Wertheimer and Lecuire (1953)—107 cases operated on in twelve years. They thought that some of the effects of the operation were due to trauma to the blood supply of the cord. The results led them to think that there was 'no precise systematization' in the pathways that they were dividing. They also found objective changes in pain and thermal sensibility in only 30 per cent of cases. They thought 'that the crossing of the midline . . . extends over five or six segments'. They therefore stated that a myelotomy in the upper thoracic cord would be useless for pain in the thorax, and in fact found that a myelotomy at the third to fifth thoracic segments would stop pain in the lower limbs, pelvis and perineum. The experience of Mansuy and coworkers in their series of 20 cases was that a myelotomy between the fourth and sixth thoracic segments cured pelvic pain, but to remove pain in the lower limbs, the incision had to be further caudal.

Thus it was realized early by neurosurgeons performing this operation that cutting the decussating fibres does not necessarily cause a band of loss of sensibility of spinothalamic type; that any sensory loss obtained is further caudal than was originally expected; and that the pain of the lesion for which the operation is being undertaken can be removed, even without causing any sensory loss. Since that time, it has been realized that the opposite situation also occurs: even when the sensory loss is obtained, the pain may not be relieved. Putnam (1934) had previously found that the pain could be relieved without there being any sensory loss, for he recorded 'the perception of pinprick returned a week or two after the operation, but the spontaneous pain did not reappear'.

Lembcke (1964) always observed a cuirass of sensory loss, and he sometimes found that prolonging an incision by one segment relieved a pain that had previously been unaffected. His operations were in the cervical cord, the most caudal segment divided being the first thoracic. He considered that the fibres cross more or less transversely within one or two segments of their cells of origin.

Šourek (1969) showed in a photograph of a transverse section of the cord that his myelotomy incision had passed completely through the midline of the cord. He obtained a girdle-shaped region of 'no sensation to pinprick' within the segments to be expected, and never far caudal to the commissurotomy level. He stated 'The original spontaneous pain disappeared even from those dermatomes in which normal sensation to pinprick was preserved', and in one case 'the analgesic girdle-shaped area practically disappeared six months after surgery' without recurrence of the pain. In all his 25 patients, 'the area from which the spontaneous pain disappeared postoperatively was considerably larger than the girdle-shaped area in which the loss of pain and temperature sensation was proved by conventional methods'. Most of his myelotomies were between the tenth and twelfth thoracic segments, the highest being between the sixth and eighth thoracic and the lowest between the twelfth thoracic and second lumbar segments. His hypothesis for the success of the operation was that fibres of both spinothalamic and posterior columns were damaged by the midline incision, and that any explanation based on dividing the spinothalamic fibres alone was inadequate. But it must be remembered that an incision made through the posterior columns would be likely to damage the most medial fibres of these columns, which come from the most caudal region of the body, whereas the spinothalamic fibres divided are most likely to be those from the local region of the body.

Lippert *et al.* (1974) reported successful relief of pain, although they never obtained complete loss of pain sensibility on testing. They found hypoalgesia consisting of 'only a small band related to the level of spinal commissurotomy'; this was present in 5 out of 9 patients.

Many surgeons have been struck by the caudal extent of the sensory loss and relief of the pain of the carcinoma due to the myelotomy incision. Even more surprising is the cranial extent of decreased pain sensibility, which can be considerably cranial to the incision. King (1977) reported in his Case 6 that there was objective loss of pain sensibility as high as the seventh to the eighth thoracic segments, with an incision extending from the tenth thoracic to the first sacral segments. In all his cases he observed an unexpected caudal extent to sensory loss and pain relief. With regard to the caudal extent, Cook and Kawakami (1977) relieved perineal pain in two patients by incisions from the eighth to the twelfth, and from the ninth to the eleventh, thoracic segments; these incisions did not cause analgesia nor therm-anaesthesia in these segments of the body. Of the cases reported here, 2 showed more extensive sensory loss than would have been expected from the length of the incision. In Cases 2 and 3, the caudal extent of decrease in pain sensibility and in Case 3 the cranial extent were also greater than might have been expected from the length of the incision.

Thus one of the features of this operation is the caudal extent of decreased pain and thermal sensibility and the more surprising cranial extent, where the loss can be further cranial than the cranial end of the incision. It is reasonable to believe that when there is a cuirass of loss of nociception and thermoreception there is division of spinothalamic fibres. It seems that these fibres do not cross the cord in a very oblique manner, for if they did, there would be a short region of total sensory loss with larger regions of partial loss cranial and caudal to this band of total loss. As the cranial border of sensory loss of spinothalamic type is at least as high as the midline incision, a large proportion of the crossing fibres must have been cut. It has been learned from the operation of anterolateral cordotomy that when this incision cuts across the anterior and lateral white matter right up to the grey matter at any segmental level, the level of sensory loss is up to the incision or just one segment lower. This combined evidence shows that a large proportion of the fibres cross within one or two segments of their cells of origin. However, this concept does not account for the loss of pain and thermal sensibility far caudal to the lower level of the incision. Many fibres subserving these forms of sensibility cannot have been cut by the short myelotomy incision. We cannot adequately explain these facts.

Our inability to explain the cranial and caudal extent of the sensory loss is as nothing to compare with our inability to explain, on present anatomical concepts, the findings of Hitchcock (1970, 1974) and Schvarcz (1976, 1977). Their findings show that the effects of the operation cannot be accounted for on the basis of merely cutting spinothalamic fibres. Hitchcock (1970) found that an incision of 'only a part of one segmental decussation', made 'at the first cervical segment or the cervicomedullary junction' produced well-marked spinothalamic sensory loss which could extend over almost the entire body and relieve pain very far caudal to the incision. In his Case 1, in addition to the spinothalmic sensory loss over the left side of the face and both upper limbs, there was also a second region of bilateral sensory loss, further caudally, below the knees. In one of his cases, there was 'complete loss of pain to pinprick over the whole body' except for the central region of the face, and in another, except for the hands and feet. The observation of similar sensory loss in the face, leaving a central region round the nose and mouth intact, can be explained by the incision high in the cervical cord cutting quintothalamic fibres as they cross from the caudal part of the trigeminal nucleus. Nothing quite like these sensory findings had ever been described before.

A few of Schvarcz's 45 patients (1976) had analgesia to pinprick of an unexpected distribution, on one or both arms, or in the trigeminal territory, or more rarely, in the lower half of the body. Later he reported (1978) that hyperpathia was often removed and that noxious stimuli were no longer painful. Schvarcz also stimulated (1977) 'the central canal region' in conscious patients and obtained 'a basic pattern of responses . . . related to stimulation of the base of the dorsal funiculi'. This consisted of paraesthesiae starting at the soles of the feet and spreading to the dorsal aspect of the legs; sometimes there were 'bilateral burning truncal sensations'; this latter sensation must be classified as pain.

The extraordinary observations first reported by Hitchcock have now been repeatedly confirmed by other neurosurgeons. Papo and Luongo (1976) made lesions 'between the upper posterior rootlet of C2 and the lower one of C4 segment'. Their operation relieved the pain completely or partially in 5 patients whose pain was in the upper limbs and/or thorax, in 4 patients whose pain was in the lower limbs and/or sacral region, and relieved the pain in the perineum in 1 patient. In 3 of their 10 patients there was the expected band of change in sensibility, although it was only 'mild hypoalgesia'. In 3 patients there was no objective sensory loss and yet the operation successfully removed the pain. Papo and Luongo, like Hitchcock, found that the cervical myelotomy relieved the pain wherever it was situated.

The large extent of sensory loss due to short incisions in the upper cervical cord and Schvarcz's observations on stimulating the central canal region led both Hitchcock (1970) and Schvarcz (1976, 1978) to conclude that there were polysynaptic pathways within the central grey matter able to conduct impulses originating in most of the body. They also suggested that this pathway explained the return of pain after an anterolateral cordotomy. Many workers in this field have concluded that pathways other than spinothalamic and spinoreticulothalamic for the conduction of impulses causing pain must exist. These will now be considered.

An alternative pathway most often proposed is spinospinal fibres, running either within the grey matter or in the perigriseal white matter. Anatomical evidence concerning the intrinsic fibres of the grey matter was reviewed by Nathan and Smith

(1959). Little appears to have been added since Laruelle (1937) wrote 'L'association plurisegmentaire est réalisée, non seulement par les voies cordonales connues, mais par un système de fibres intrinsèques de la substance grise; et les confèrent une fonction conductrice propre à la substance grise de la moelle.' This chain of intrinsic fibres could constitute the pathway suggested by Hitchcock and Schvarcz; for some of the intragriseal fibres might well be damaged by the myelotomy incision; but it is unlikely that all the fibres of this system would be destroyed. Those in the neighbourhood of the central canal would be most likely to be damaged. Others, lying more laterally, might be destroyed when the incision is oblique or off centre. It is unlikely that the same fibres would be affected in all myelotomy lesions.

It might be thought that syringomyelia would throw light on the effect of a lesion of the commissures and of the central grey matter. Although cavitation may start in this region, by the time the patient dies there is extensive loss of pain and thermal sensibility. By that time, the cavitation is enormous and destroys a large number of pathways.

Karplus and Kreidl (1914, 1925) reviewed the large literature on spinal cord pathways for nociception. From carrying out bilateral hemisections in the cat, they concluded that there was 'in addition to the long tracts a chain of short tracts used for pain conduction'. They postulated that this pathway was of particular importance for the anogenital region. If there is such a pathway in man, this may play a role in the persistent spontaneous pains that occur in the rectum, vagina and perineum. There is a footnote at the end of their 1914 paper saying 'Our findings in cats led us to undertake similar experiments in monkeys. In four monkeys, hemisections on the two sides were performed at one operation. After the operation, no trace of conduction of pain could be found.' This operation of two hemisections of the cord carried out at different levels thus produced different results in the monkey from those in the cat. Although Karplus *et al.* were reluctant to conclude from their experiment on the monkey that nociception was conducted in the tracts of the white matter, it is difficult to draw any other conclusion.

It has sometimes been suggested that the pathway for conduction of visceral pain consists of short chains of neurons in or near the grey matter. Evidence for the cat and dog will now be presented, but it must be emphasized that in man bilateral anterolateral cordotomy stops all visceral pain, even the pain of acute obstruction or of forcible dilatation of the renal pelvis. In the cat, Davis (1922) attempted to define the spinal pathway for the visceral afferents responsible for the changes in blood pressure and respiration caused by a painful stimulus. From making various spinal lesions, he concluded 'It is reasonable to presume that the impulses arising from the viscera . . . are conducted upwards by relays of short spinal paths with synapses in the gray matter of the spinal cord.' In some further experiments carried out with Hart and Crain (Davis *et al.*, 1929), on the dog, he showed that impulses causing pain from the viscera ran in the central grey matter. Kletzkin and Spiegel (1952), performing bilateral hemisections of the cord in the cat and injecting barium chloride into the femoral arteries, concluded that this arterial pain 'was conducted by chains of short neurons'.

Nathan (1956) and Noordenbos (1959) came to the conclusion from their cases of anterolateral cordotomy in man that there must be alternative pathways in or near the grey matter. Their views were based on certain forms of sensation occurring after anterolateral cordotomy. Nathan suggested that one alternative could be Lissauer's tract, and another could be an intragriseal pathway connecting the cells of origin of the spinothalamic tract, both transversely and longitudinally. Noordenbos devoted a large part of his book on pain to this subject. He concluded that there must be a network of spinospinal neurons forming a multisynaptic afferent system in the perigriseal white matter, projecting to the thalamus. Noordenbos postulated that this network receives collaterals of small posterior root fibres and of long afferent tracts.

It seems unlikely to us that propriospinal fibres near the grey matter of the anterolateral columns conduct impulses related to pain. We looked into this question in our cordotomy material, examining the cases in which there was complete loss of pain and thermal sensibility in a restricted part of the body and in which the lesion did not involve the deeper white matter, where perigriseal fibres run. In these cases, sensory loss could not have been denser had the lesion extended right into the grey matter. These transverse sections of cords following cordotomy were illustrated in a previous paper (Nathan and Smith, 1979). As far as we know, evidence that perigriseal fibres concerned with conduction of nociception has never been produced in man, although the following work does show that fibres near the grey matter in the cat and the monkey can have such a function.

Richards *et al.* (1966) and Shealy *et al.* (1966) stimulated various fibre groups of peripheral nerves of upper and lower limbs and recorded the evoked responses from the lateral perigriseal region contra- and ipsilaterally. The region from which they chose to record was deeper than the spinothalamic and spinoreticular tracts. They then carried out commissural myelotomies of various lengths to see what proportion of the evoked responses was blocked by the midline incision. They found, as expected, that a certain length of myelotomy was necessary to remove this contralateral evoked response. They also found that evoked responses were occurring perigriseally ipsilateral to the input. From their recordings, they concluded that fibres responsible for this evoked response crossed somewhere cranial to the midthoracic cord and caudal to the upper medulla oblongata. The evoked responses from stimulating the nonmyelinated fibres of the peripheral nerves ran both contra- and ipsilaterally, with the probability that they ran mostly ipsilaterally. 'In three rhesus monkeys and in one tree shrew, we have demonstrated ipsilateral responses exactly the same as those in cats and found no apparent differences.' They thought that these perigriseal fibres were a part of a short fibre multisynaptic system, and they too suggested that the return of pain after anterolateral cordotomy was due to the use of this ipsilateral pathway.

Traditional anatomy has never regarded fibres of the posterior columns as a nociceptive pathway. The reasons, no doubt, are that the operation of anterolateral cordotomy, which leaves the posterior columns intact, removes all sensibility of pain as well as of warmth and cold. On ordinary clinical examination diminution in pain sensibility is not seen with lesions of the posterior columns. But Kroll (1930), who studied Foerster's cases, found a decrease in pain spots in the expected region after division of the fasciculus gracilis; this is important and forgotten evidence. Although Foerster (1936) wrote that touching the posterior columns and the operative division of the posterior columns always caused severe pain, a great deal of knowledge of the effect of electrical stimulation of the posterior columns has been acquired since that time, and this does not cause pain.

The fasciculus gracilis was divided in the monkey by Vierck *et al.* (1971). This caused a lasting decreased reactivity to noxious stimuli ipsilaterally, and they posed the question as to whether 'these lesions could have interrupted pain fibres'. Petit and Burgess (1968), who examined the dorsal column projections of receptors connected to myelinated fibres in the cat, favoured the opposite view; they found no high-threshold fibres from the posterior roots in the posterior columns, and they stated that this finding was 'consistent with the idea that this pathway has little to do with pain'.

A further group of fibres running in the posterior columns are the postsynaptic fibres, taking origin in the posterior horns; they have been studied in the cat by Uddenberg (1968) and by Angaut-Petit (1975*a*, *b*). These large myelinated fibres were activated by cooling the skin, by heat and by noxious stimuli. However, Brown and Fyffe (1981) did not confirm that any of these fibres were activated by noxious stimulation.

The spinocervicothalamic tract has been proposed as a pathway concerned with pain in the cat and dog. Dart and Gordon (1970, 1975) showed in the cat that fibres of this tract carried impulses caused by noxious stimulation. But most workers now (Ha, 1982) have concluded that this is a pathway for mechanoreception. In man, the lateral cervical nucleus, an essential part of this pathway, is rudimentary. Truex *et al.* (1970) found that it consisted at most of a very few cells. One of the present authors (M.C.S., jointly with P. Deacon) has confirmed these findings in 47 human cords. This pathway, if it exists in man, is thus unlikely to be of much importance.

We consider that the evidence from myelotomy and anterolateral cordotomy does not inevitably lead to the conclusion that there is a second afferent pathway always available for the conduction of impulses causing pain. If this were so, it is difficult to see how spinothalamic cordotomy could ever be successful. It must be remembered that impulses from the body caudal to the myelotomy incision are running in both spinothalamic tracts in the anterolateral columns, and that these tracts are not involved in the midline incision. It may then be questioned whether the pain-relieving effect of the myelotomy incision in the grey matter blocks impulses entering into, or in, or leaving the spinothalamic complex. Mansuy *et al.* (1944) and Hitchcock (1970) reported that the relief of pain may not occur immediately after the myelotomy and that it may take one or more days to come on. These observations and the other observations discussed above strongly suggest that the relief of pain achieved in this operation is not due merely to division of an afferent pathway.

Post-mortem examinations are necessary to confirm the actual lesion made by the surgeon so that this can be correlated with the effect of the operation. Very few have been obtained. Šourek (1969) published a photograph of a transverse section showing the myelotomy lesion: the cord had been divided into two halves by a narrow midline incision. The photograph of the cord section published by Hitchcock (1970) shows a narrow electrode track; it was not in the midline but was 'parallel to the posterior midline septum and anterior sulcus'. Most of the other lesions have been larger. Already in 1953, Wertheimer and Lecuire had reported their post-mortem findings, although they gave no photographs of the cords. They found that 'The section was not absolutely in the midline; the anatomical lesions were longer than the limits of the surgical intervention'. They observed 'important vascular alterations, which caused necrosis and oedema at a distance'. Lippert *et al.* (1974) obtained two post-mortem examinations, and published a photograph of one of the cords through the myelotomy lesion. There was a great deal of damage to the medial part of both posterior columns. King (1977) examined two of his lesions. The anterior commissurotomy was complete. He found 'demyelinization and gliosis in the medial dorsal columns and in both anterolateral quadrants at levels rostral to the myelotomy. At the level of the myelotomy there was a moderate amount of central cord change, extending into the medial and deep portions of the dorsal horns and the central gray matter, where neurons were very sparse or absent.' This description accords with the post-mortem findings reported here. It is probable that a lesion which is not in the midline and which involves the posterior and anterior horns would cause more vascular damage than a lesion restricted to the midline.

Asymmetry of Sensory Loss after Myelotomy

The sensory loss after this operation may differ on the two sides of the body. This was seen in Cases 2 and 3. It is also shown by Hitchcock (1970) in his Cases 3, 4 and 5, and in one of the cases reported by King (1977). In some cases asymmetry appears clearly as recovery in sensibility proceeds.

This asymmetry could be accounted for by variations of a midline incision that might inadvertently be made. Some of these are illustrated diagrammatically in fig. 7. The ideal midline incision is shown in fig. 7A. Fig. 7B shows an incision that is off-centre but parallel to the midline. Fig. 7C and D illustrate two varieties of oblique incision, one remaining on the one side of the midline, the other crossing the midline. In the off-centre and the oblique incisions remaining on one side of the midline, it is likely that the majority of fibres of the spinothalamic complex divided are those taking origin on that side. In the case of the oblique incision crossing the midline, the fibres most likely to be divided are those arising on the opposite side. There could be a combination of these varieties, for an incision may not remain absolutely in the midline throughout its extent.

The depth or anterior extent of the incision is another factor determining the sensory loss. Some surgeons aim to pass the instrument through the cord to reach the anterior median fissure. Others aim not to divide tissue anterior to the anterior white commissure. If a predetermined depth of incision is made and the incision is off-centre, oblique but remaining on one side, or oblique crossing from one side to the other, then the depth of the incision would be too short to involve many of the anteriorly lying decussating fibres.

These suggestions are put forward on the basis of cases in the literature and of the histological evidence in this paper, and also of other post-mortems of myelotomy lesions we have examined. In the latter cases, the survival was too short for adequate assessment of the clinical state, and so they are not included in this paper.

The Borders of the Area of Sensory Loss due to Lesions of the Spinal Cord

In transverse lesions of the spinal cord, in anterolateral cordotomy and after commissural myelotomy, where the border of sensory loss is on the trunk, it passes around the trunk at right angles to the long axis of the body. This is not to say that the level of the border is an absolutely straight line, but it does not conform to the anatomical distribution of a posterior root. After a posterior rhizotomy, the sensory loss follows the slope of the intercostal space. With spinal lesions, the border is often

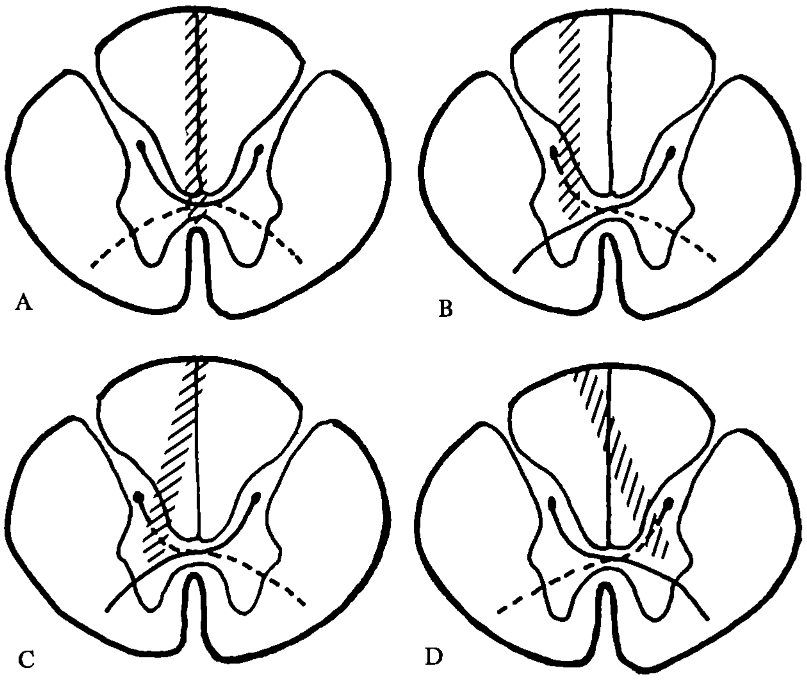

FIG. 7. Diagram showing some possible locations of myelotomy lesions, indicating which spinothalamic and spinoreticulothalamic fibres each lesion is most likely to divide. Lesions shown by hatching, degeneration of nerve fibres by dotted line.

lower posteriorly than anteriorly and, after myelotomy, it may slope markedly caudally towards the midline at the back. Examples of the sensory loss are shown in figs. 4, 5 and 6.

Some Differences Between the Effects of Commissural Myelotomy and Anterolateral Cordotomy

After anterolateral cordotomy the sensory loss can be complete for warm, cold, and noxious stimulation. In our series of cordotomies, one patient had complete bowel obstruction which caused no pain whatsoever. In some of our patients, formic acid was painted on decubitus ulcers and caused no sensation. After myelotomy, this degree of sensory loss is rarely seen. A typical example was one patient who said 'I feel pain but it is muffled; something is over it.' In these patients repeated hard pinprick usually causes pain and some thermal stimulation is usually felt.

After myelotomy, the state of sensory loss fluctuates, both in its extent and degree. Further, the boundaries of the sensory loss are not clearcut; they are vaguer and tend to change during examination. This changing picture is not found after cordotomy; if recovery of sensibility does occur, it takes months or years. It always seems to occur after myelotomy, starting within weeks of the operation.

What was striking in Case 2 was the asymmetry of the recovery of sensory loss. While there was still fairly marked loss of nociception and thermoreception on one side of the body, recovery was almost complete on the other. Also, the back and side became almost normal while the front of the body still had objective sensory loss. Neither of these kinds of sensory loss have ever been seen in our 41 cases of bilateral anterolateral cordotomies.

Diminution in tactile sensibility may be more obvious after myelotomy than after cordotomy. This is the opposite of what would have been expected. Minimal though it is after anterolateral cordotomy, it would have been expected to be even slighter after myelotomy, as the loss of pain and thermal sensibility is less. Touch would have been anticipated to follow suit. This diminution in tactile sensibility is not due to damage to posterior column fibres, for the fibres of these columns that are involved in the lesion are those lying medially, coming from segments caudal to the level of the incision.

Accurate Localization of Pinprick and Thermal Stimuli via *the Spinothalamic Tract*

When the operation of commissural myelotomy damages the posterior columns, there is a region of the body deprived of posterior column fibres and supplied by fibres of the spinothalamic tract. In this region warm and cold stimuli are accurately localized. This was previously shown for radiant heat stimuli by Nathan and Rice (1966).

Cold and warm stimulation in the cases reported here was carried out so that there was no tactile element. Noxious stimuli consisted of pressure with the algometer, pinprick and two-point discrimination with the actual sharply pointed two-point stimulator used by Head and Holmes. What was most curious was that two-point discrimination was accurate when two sharply pointed stimuli were used to cause pain. For instance, discrimination of these points was achieved at a 6 cm distance on the front of the legs and 4 to 5 cm on the feet. Yet in these parts of the body two-point discrimination of purely tactile stimuli could not be undertaken, as the patient often did not even know which leg was being touched. Thus it was clear that pinpoint discrimination was made on its painful and not on its tactile features.

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THE HORMONAL RESPONSES TO GENERALIZED TONIC-CLONIC SEIZURES

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SUMMARY

We studied the hormonal responses to a generalized tonic-clonic convulsion in 20 patients with idiopathic or posttraumatic epilepsy (6 patients) or alcohol-withdrawal seizures (14 patients). We found an increase shortly after the seizure in plasma levels of ACTH, beta endorphin, beta lipotropin, prolactin, and vasopressin, and a later increase in plasma cortisol. There was no significant change in levels of growth hormone, luteinizing hormone, follicular stimulating hormone, or plasma renin activity. An increase in plasma ACTH level was accompanied by a rise in beta lipotropin and beta endorphin, and followed by a rise in plasma cortisol. In 2 patients there was no postictal increase in plasma prolactin, despite changes in other hormones. There was no difference in the nature or time course of the hormonal changes in patients with alcohol-withdrawal seizures and those with seizures from other causes.

The mechanisms subserving these changes are unknown. Nonspecific stress influences the release of certain hormones, but the absence of a significant growth hormone response suggests that this was probably not responsible for our findings. It is possible that the generalized neuronal discharge of a seizure stimulates the hypothalamus either directly, through specific neurotransmitter changes, or through the release of other substances. One possibility that we are investigating in experimental animals is that endogenous opioids are involved, especially in the release of prolactin.

INTRODUCTION

Seizures may have profound hormonal manifestations, and serum prolactin changes have been used to distinguish generalized tonic-clonic seizures from other causes of brief stereotyped disturbances of cerebral function (Trimble, 1978; Höppener *et al.*, 1981). Although serum prolactin increases fifteen to thirty minutes after a tonic-clonic seizure and then rapidly reverts to normal, it is not clear how reliably such changes distinguish between a true and a simulated ('nonorganic') seizure. The basis of this response is also uncertain, possible mechanisms including the activation of specific pathways, the occurrence of a generalized nonspecific cerebral discharge, and a stress phenomenon. Further, apart from the prolactin response, the other hormonal changes that follow a major seizure have not been

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clearly defined. It was with these points in mind that we undertook the present study to characterize the hormonal response to a single generalized convulsion.

METHODS

We studied the responses of 20 patients (18 males, 2 females), ranging in age between 23 and 62 years (mean 45 years), to a total of 24 single generalized tonic-clonic seizures. These seizures were related to alcohol withdrawal in 14 patients, and were idiopathic or posttraumatic in 6. There were no accompanying neurological or general medical disorders, except in one patient with a long history of excessive ethanol intake, who was mildly demented. Three patients were on phenytoin and one also took phenobarbitone. No patient was taking any other medication, or was under treatment for any major psychiatric disorder. Blood glucose was checked routinely with Dextrostix when patients first presented, and none with hypoglycaemia was admitted to the study.

We tried to obtain blood samples at fixed intervals of time after the seizure, but there was inevitably some variation in this regard. Samples were obtained with the patient recumbent, and efforts were made to obtain them within 10 and 30 min of the seizure, and then 1, 2, 3, 4 and 24 h after its onset. However, we were not able to collect samples at these times in every patient, and sample size sometimes limited the number of hormones that could be assayed. No patients received any drugs during the 24 h period of our study except for those already receiving anticonvulsants, which were continued as before, but even in these 3 cases, the next dose was not taken for at least 6 h after the seizure.

Blood was collected into heparinized vacuum tubes for determination of plasma renin activity (PRA) and into EDTA-containing tubes for measurement of cortisol, growth hormone (GH), prolactin, vasopressin, follicle stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotrophic hormone (ACTH), beta lipotropin and beta endorphin. Plasma was promptly separated from blood cells at 5° C, aliquoted for the various hormone assays, frozen and stored at −70° C until assayed. Aliquots for assay of ACTH, beta lipotropin and beta endorphin received 500 kallikrein inhibitory units of aprotinin per ml of plasma prior to freezing. All hormone determinations were performed by radioimmunoassay. Prolactin, GH, FSH, LH and ACTH were assayed using kits provided by the National Pituitary Agency. Radioassay kits for PRA, cortisol and vasopressin were obtained from New England Nuclear (Boston), Nuclear-Medical Laboratories (Dallas) and Immuno Nuclear Corporation (Stillwater) respectively. The assays for ACTH, beta lipotropin (Wiedemann *et al.*, 1977) and beta endorphin (Wiedemann *et al.*, 1979) were set up simultaneously using plasma extracts rather than whole plasma. For extraction, 2 ml of plasma, cleared of precipitate by centrifugation, were vortexed for 1 min with 10 mg of QUSO G-32 microfine semicolloidal quartz adsorbent (Calbiochem, San Diego). After centrifugation for 15 min at 4000 g, the pellet was washed with 2 ml of water and then extracted by vortexing for 30 s with 2 ml desorbent consisting of 0.05 M HCl, 0.25 per cent bovine serum albumin, 0.1 per cent Triton × 100, 0.02 mM phenylmethylsulfonyl fluoride and 0.1 per cent thimerosal. The supernate recovered after a 45 min centrifugation at 5° C and 4000 g was stored at −70° C until assayed.

None of the assays for each of the hormones showed significant cross-reaction with any of the other tested hormones. The sensitivity of all the assays employed was such that the hormonal levels to be measured fell within the sensitive portion of the standard curves.

In analysing the findings, two repeated measures analysis of variance models were fitted to the hormone data for all cases combined: a two-factor model that included diagnosis (alcohol withdrawal *vs* other causes), time, and the interaction between diagnosis and time, and a one-factor model that included only time. The one-factor model was also fitted to data for alcohol and nonalcohol related seizures separately. These models were fitted (Mr R. Cohen) both to the original hormone values, and also to log transformed values as these reduced the heterogeneity of the variance. The Bonferroni modification of Student's t test was used to compare mean values at each time point with baseline mean values, which for the present purposes were taken as the levels measured 24 h after the seizure.

RESULTS

Using the two-factor model of repeated measures analysis of variance, we did not find a significant difference in mean hormonal levels, or in the time course of the various hormonal changes, between patients with alcohol withdrawal seizures and those with seizures from other causes. These conclusions were the same regardless of whether the statistical analysis related to data in the original units of measurements or to log transformed data. Accordingly, we combined the data from the two patient groups and reanalysed them using the one-factor model that included only time as an independent variable. We found a significant change in mean level over time of ACTH ($P = 0.008$), beta endorphin ($P = 0.0001$), beta lipotropin ($P = 0.002$), cortisol ($P = 0.018$), and prolactin ($P = 0.0001$), regardless of whether the original or log transformed data were analysed. Analysis of the original data suggested a significant change with time in vasopressin level ($P = 0.04$), but the change failed to reach statistical significance when the log transformed data were used ($P = 0.35$). The log transformation appears to have increased the variation relative to the mean in this instance, making the test on log transformed data less sensitive. The opposite was true for FSH, a change occurring with time that was statistically significant for the log data ($P = 0.036$) but not for the original values ($P = 0.26$). No significant change occurred in levels of GH, PRA, or LH.

We used the Bonferroni modification of Student's t test to compare the mean hormone level at each time point with the 'baseline' value, that is, the mean value found twenty-four hours after the seizure. A critical value for each set of comparisons was chosen to keep the maximum probability of a type 1 error less than, or equal to, 0.05. The mean square error and its associated degrees of freedom from the repeated measures analysis of variance was used in the denominator of the t statistic for each comparison. Using the mean square error from the two-factor analysis of variance yielded the same results as using that from the one-factor model. We found significant elevations above baseline for plasma ACTH, beta endorphin, beta lipotropin, cortisol, prolactin, and vasopressin, at specific times following the seizure, as illustrated in figs. 1, 2 and 3.

It is possible that our statistical analysis failed to reveal any difference between alcohol and nonalcohol-related seizures because of the small number of subjects in the latter group. We therefore examined the data from individual patients. An increase in plasma ACTH level was accompanied by a rise in plasma beta lipotropin and beta endorphin within ten minutes of the seizure, and accompanied or followed by a rise in plasma cortisol. It was a consistent finding in both groups.

The group data indicated that the plasma prolactin level showed a sharp rise in the first thirty minutes after the seizure (generally to between 300 per cent and 400 per cent of baseline values in individual cases), remained elevated at one hour, and subsequently did not differ significantly from the baseline levels. In 2 patients, however, there was no change in plasma prolactin levels following their seizures, which were unequivocal generalized tonic-clonic convulsions. In one of the patients,

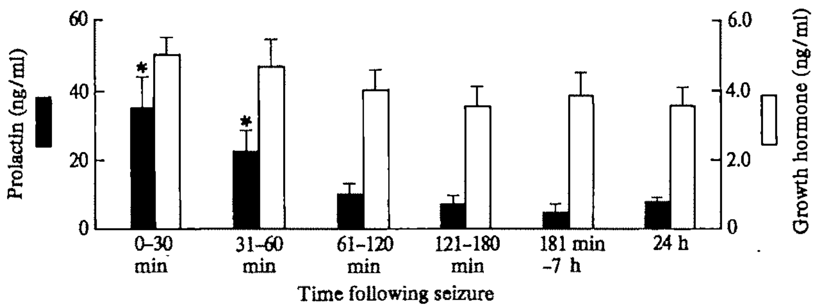

FIG. 1. Plasma prolactin and GH responses to a single tonic-clonic seizure. Arithmetic means (± standard error) for the group of patients studied are shown. Asterisks indicate significant differences from baseline values ($P < 0.05$). The prolactin response is maximal in the first 30 min following the seizure, but there is no significant change in GH levels.

whose seizure was related to alcohol withdrawal, it was not possible to obtain a blood sample until more than thirty minutes after the seizure, and this may have accounted for the apparent lack of a prolactin response but preserved cortisol response. In the second instance, however, an early blood sample was obtained, and the seizure, which was not related to alcohol withdrawal, led to changes in plasma cortisol and plasma catecholamines such as we have described elsewhere (Simon *et al.*, 1984).

Although the grouped data showed no significant change in plasma LH and FSH with time, following either alcohol or nonalcohol-related seizures, review of the individual data did suggest a response in some cases. Thus in 4 of 10 instances (including one of 3 nonalcohol-related seizures) the LH showed an increment within thirty minutes of the seizure compared to later values, while in 7 instances (2 of which were unrelated to alcohol) an unequivocal or suggestive increase in FSH occurred over this same time course.

The plasma GH data for the group suggested an early postseizure elevation, but this failed to reach statistical significance. Review of the individual data suggested that in 8 patients there was indeed no change over time, whereas in 8 others the GH level did appear to be elevated after the seizure, subsequently declining with time. Among both the patients with alcohol-related seizures and those with seizures from other causes, there were some patients who seemed to show an initial GH response and others who did not. We therefore examined the response curves of GH for the two groups (apparent responders and nonresponders), but found no significant differences in their mean responses or in their time trends.

We found a clear increase in plasma vasopressin level in all patients in whom samples had been obtained within thirty minutes of the seizures for assay, regardless of whether the seizure related to alcohol. The PRA data from individual subjects showed that regardless of their cause, seizures induced no change in PRA activity.

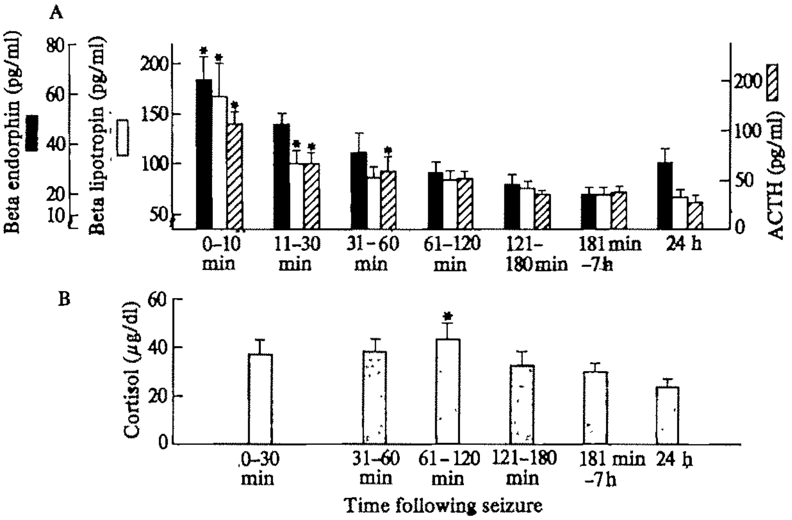

FIG. 2. The time course of changes in plasma ACTH, beta endorphin, beta lipotropin (A) and cortisol (B) concentrations after a single tonic-clonic seizure. Arithmetic means (± standard error) for the study group are shown. Asterisks indicate significant differences from baseline values ($P < 0.05$). The cortisol response occurs 1 to 2 h after the seizure, clearly following that of ACTH, as would be expected.

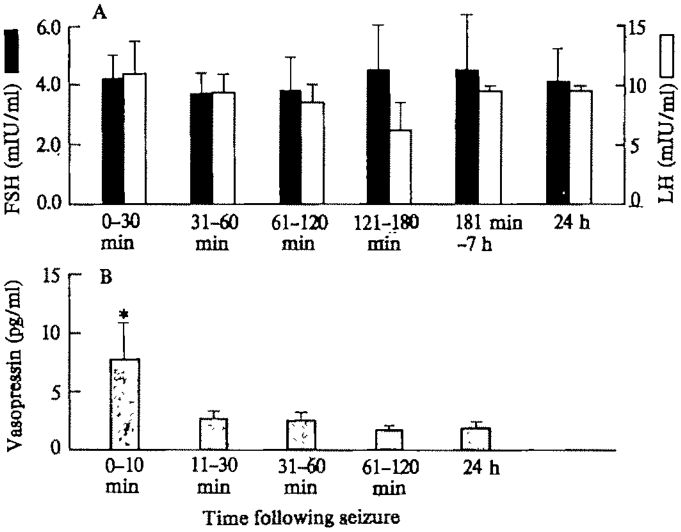

FIG. 3. Plasma FSH and LH (A), and plasma vasopressin levels (B) at various time intervals after a single tonic-clonic seizure. Arithmetic means (± standard error) for the group of patients studied are shown. The asterisk indicates a significant difference from baseline value ($P < 0.05$). There is no significant change in FSH or LH levels with time, but plasma vasopressin concentration is markedly increased within 10 min of the seizure, thereafter reverting to baseline values.

DISCUSSION

Serum prolactin rises rapidly after electroconvulsive therapy (Öhman *et al.*, 1976; O'Dea *et al.*, 1978), or a spontaneously occurring generalized seizure, reaching a peak between fifteen and twenty-five minutes after the seizure (Trimble, 1978) and reverting to normal in about two hours (Abbott *et al.*, 1980). These prolactin changes have aroused particular interest as a possible means of distinguishing tonic-clonic seizures from simulated attacks or 'pseudoseizures', since a marked prolactin increase does not follow the latter (Trimble, 1978; Höppener *et al.*, 1981). A mild increase does accompany heavy physical exertion (Höppener *et al.*, 1981), however, and could therefore occur after a pseudoseizure characterized by marked flailing of the limbs. Such a finding may then lead to diagnostic confusion because the rise in serum prolactin following a true tonic-clonic convulsion is sometimes similarly modest (Höppener *et al.*, 1981). Indeed, Oxley *et al.* (1981) reported a patient in whom serum prolactin level showed a significant increase shortly after an attack that by clinical and EEG criteria was nonepileptic in nature.

An additional difficulty that may arise if serum or plasma prolactin measurements are used to distinguish genuine generalized seizures from simulated attacks is illustrated by our findings. Although the prolactin changes in our group of patients had a similar time course to that described by others, there was no rise in two of our patients, following attacks that clinically were unequivocal tonic-clonic seizures and which led to other hormonal changes. Similar findings have been noted in rare instances by others, but have been neglected or discounted. Thus Öhman *et al.* (1976) found in 1 of 9 patients that electroconvulsive therapy did not produce a significant prolactin response, as did Dana-Haeri *et al.* (1983) in 1 of 15 males after a spontaneous seizure. Again, Abbott *et al.* (1980) observed that in 2 of 5 patients followed serially after a seizure, there was no clear change in prolactin level. These latter authors tried to explain away their findings—in one patient the seizure was said to be 'atypical' (with continuous minor clonic twitching and coma for thirty minutes before termination with diazepam), while in the other, an elderly woman, it was suggested that a difference in hypothalamic function (compared to younger male patients) was responsible.

These various findings indicate that complete reliance cannot be placed on the prolactin response in the distinction of tonic-clonic from simulated seizures.

The mechanism subserving the prolactin change is not known. One possibility is that it relates to nonspecific stress, which may certainly influence the release of prolactin (Noel *et al.*, 1972) and also other hormones. Plasma levels of ACTH and beta endorphin (Guillemin *et al.*, 1977), and of cortisol, are known to rise with stress. Previous studies have shown that electroconvulsive therapy increases plasma cortisol (Bliss *et al.*, 1954) and ACTH (Allen *et al.*, 1974; Ylikorkala *et al.*, 1976). We found a postseizure elevation in plasma cortisol preceded by a marked increase in plasma ACTH, beta endorphin and beta lipotropin, all of which have a common precursor (Eipper and Mains, 1980). Harms *et al.* (1975) reported that dexamethasone blocked, whereas adrenalectomy potentiated stress-induced prolactin release in rats, and this is consistent with the presence of a common pathway or mechanism involved in pituitary release of prolactin and ACTH.

Plasma GH may also rise with acute stress (Brown and Reichlin, 1972). However, we did not find a consistent postseizure rise in GH, although in several of our patients a clear rise did occur. The previously published data concerning changes in this hormone following electroconvulsive therapy are conflicting. Thus some authors have reported no change in either fed (Ryan *et al.*, 1970) or unfed (O'Dea *et al.*, 1979) subjects, whereas others describe a significant increase within thirty minutes of electroconvulsive therapy (Vigas *et al.*, 1975; Skrabanek *et al.*, 1981). The absence of a consistent GH response suggests that the other hormonal changes are not part of a nonspecific stress reaction to the seizure. Nevertheless, it does not completely exclude this possibility, since different classes of stress may produce different patterns of hormonal response (Feldmann and Brown, 1976).

It is possible that the lack of a consistent GH response was alcohol-related, since impaired GH responses to insulin-induced hypoglycaemia are well described (Chalmers *et al.*, 1978). However, neither the grouped data nor the findings in individual cases suggested any difference in our GH findings following alcohol-related seizures and those from other causes. Moreover, we found no evidence of loss or attenuation of prolactin or corticosteroid response following the alcohol-related seizures, whereas in recently abstinent alcoholics these stress responses to insulin-induced hypoglycaemia may also be impaired (Chalmers *et al.*, 1978).

We found no consistent postictal change in LH or FSH, but in several of our male patients these hormones were elevated immediately after the seizure, perhaps because of spontaneous random fluctuations (Nankin and Troen, 1971). Ryan *et al.* (1970) also found increases in serum levels of these hormones in some but not all men, and no change in postmenopausal women, following electroconvulsive therapy. There is, however, some discord in the literature concerning changes in plasma gonadotrophins following electrically induced or spontaneous seizures. Thus, Ylikorkala *et al.* (1976) found no consistent changes whereas Skrabanek *et al.* (1981) reported a significant elevation within thirty minutes in both LH and FSH among patients other than postmenopausal women, and Dana-Haeri *et al.* (1983) found consistent elevations of LH in patients of either sex and of FSH in females only. The lack of consistent findings within and between studies has an uncertain basis, but suggests that any change in plasma gonadotrophins after seizures relates to a combination of other factors depending on the type of patients examined.

Electroconvulsive therapy causes a rapid increase in plasma vasopressin (Raskind *et al.*, 1979), and also a dramatic increase in plasma nicotine-stimulated neurophysin, which is associated with vasopressin (Whalley *et al.*, 1982). We similarly found a significant rise in plasma vasopressin following seizures in our patients.

In general, then, our results conform with and extend the results of earlier studies performed in humans receiving electroconvulsive therapy. We found that after spontaneous seizures there are a variety of hormonal changes. Although chronic alcohol consumption has several important effects on the endocrine system, our findings concerning the acute hormonal effects of seizures applied both to alcohol-related seizures and to seizures from other causes. Alcohol withdrawal *per se* may lead especially to impaired stress responses in some instances (Chalmers *et al.*, 1978), but this was not evident in the data obtained from our patients. The pattern of the endocrine response observed after seizures suggests that it is not merely a non-specific stress reaction, although, for the reasons indicated earlier, this possibility cannot be excluded with absolute confidence. Whether the endocrine response relates to generalized neuronal discharges involving hypothalamic stimulation either directly or through specific neurotransmitter changes such as follow repeated electroconvulsive shock (Grahame-Smith *et al.*, 1978; Green *et al.*, 1977, 1980; Bergstrom and Kellar, 1979; Green and Deakin, 1980), or instead relates to release of other substances—perhaps in response to stress—is unclear.

One possibility is that endogenous opioids are involved, especially in prolactin release. The rapid marked elevation that we found in plasma beta endorphin levels may then assume particular significance, although at the present time it cannot be assumed that plasma levels reflect levels in the CNS (Rossier *et al.*, 1977; Hawley and Butterfield, 1981). Morphine raises serum prolactin concentration in man (Tolis *et al.*, 1975), and recently the naturally occurring opioids, such as beta endorphin, have been shown to do so both in laboratory animals (Van Vugt and Meites, 1980) and in man (Catlin *et al.*, 1980; Reid *et al.*, 1981). Moreover, stress-induced release of prolactin is blocked by intravenous or subcutaneous naloxone (Rivier *et al.*, 1977; Rossier *et al.*, 1980; Van Vugt and Meites, 1980), and by intraventricularly administered beta endorphin antiserum (Ragavan and Frantz, 1981), suggesting that endogenous opioids are indeed involved in its release under at least those circumstances. We are therefore testing this hypothesis by further experimental studies in animals.

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EXPERIMENTAL HEMICHOREA/ HEMIBALLISMUS IN THE MONKEY

STUDIES ON THE INTRACEREBRAL SITE OF ACTION IN A DRUG-INDUCED DYSKINESIA

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SUMMARY

Antagonists of the neurotransmitter gamma aminobutyric acid (GABA) were injected at seventy intracerebral sites in the conscious monkey. Injections located in or near to the subthalamic nucleus provoked involuntary movements of the contralateral limbs. These movements had the characteristics of chorea and, when severe, resembled hemiballismus as seen following subthalamic nucleus lesions in man and monkey. Localized injections of GABA antagonists into the medial segment of the globus pallidus were without observable effect on motor activity. These observations are discussed with regard to the role of GABA in subthalamopallidal relations.

Injection of GABA antagonists at some other sites provoked different forms of dyskinesia. Injections in or near the zona incerta adjacent to the subthalamic nucleus induced torticollis and circling behaviour either in isolation or in addition to contralateral limb dyskinesia. Injections at some sites located in the lateral segment of the globus pallidus or in the putamen induced choreoathetoid or myoclonic movements, respectively.

INTRODUCTION

Hemiballismus in man is a condition characterized by gross involuntary movements of the limbs on one side of the body. The proximal appendicular and related axial muscles are particularly involved so that the movements, which may be remarkably forceful, are generally of wide excursion and have a flinging or flailing character. Other trunk muscles and the muscles of the head and neck may be additionally involved to varying extents but it is really the nature of the limb movements which epitomizes hemiballismus. The dyskinesia, which is usually of sudden onset, is virtually continuous during wakefulness, disappearing during sleep.

Hemiballismus is remarkable not only for the nature of its physical manifestation but also for the apparent anatomical specificity of the causative lesion and for the fact that a virtually identical condition can be induced experimentally in the monkey by reproduction of the human pathology. In these respects it is at present unique among the basal ganglia-related dyskinesias.

During the first half of the present century an impressive accumulation of evidence was made linking the appearance of hemiballismus in man with destructive lesions of the subthalamic nucleus, or its connections with the basal ganglia, on the side of the brain contralateral to the affected limbs (*see*, for example, Martin, 1927; Martin and Alcock, 1934; Whittier, 1947). Towards the end of this period Whittier and Mettler (1949) and then Carpenter *et al.* (1950) embarked upon a series of pioneering and now classical studies in the rhesus monkey establishing the relationship between hemiballismus and subthalamic nucleus lesions on a firm experimental basis. These workers demonstrated that fairly discrete lesions which destroyed at least 20 per cent of the subthalamic nucleus resulted in the appearance of abnormal involuntary movements of the contralateral limbs. The dyskinesia so produced was generally described as 'choreoid hyperkinesia' and in some instances was severe enough to warrant the term 'ballism'.

During recent years studies in neurochemical pathology have identified numerous neurochemical abnormalities in the post-mortem brains of the victims of various neurological disorders. These abnormalities have included regional deficiencies in certain neurotransmitters and their associated enzymes. It may be that regional neurotransmitter abnormalities in the basal ganglia and related nuclei (whether or not secondary to neuronal degeneration) are responsible for the appearance of motor symptoms in, for example, Huntington's chorea (Perry *et al.*, 1973; Bird and Iversen, 1974) but the relationship remains to be proven. This line of reasoning, however, has led to attempts to reproduce in animals the symptoms of certain human movement disorders by regional manipulation of central neurotransmission in the hope of providing new insight into the mechanisms of generation of dyskinesia.

In a previous report the present authors described an experiment in which neurotransmitter antagonists were injected into localized brain regions through an indwelling intracerebral cannula in the conscious monkey (Crossman *et al.*, 1980). Injection of the GABA antagonist picrotoxin into the region of the lateral subthalamic nucleus/medial tip of the globus pallidus in the baboon induced in the contralateral limbs a dyskinesia having many of the features of human hemiballismus. The dyskinesia was transient (with a duration of at least two hours) and could be induced repeatedly by subsequent similar injections. The trajectory of the cannula through which injections were made was oblique (approximately 60 deg to the sagittal plane) so that injection into the subthalamic nucleus was made through the intervening medial segment of the globus pallidus and the internal capsule. Thus the site of action of picrotoxin in producing hemiballismus could not be ascertained because of the possibility of drug diffusion along the injection track between the subthalamic nucleus and the medial pallidal segment.

Further studies were, therefore, undertaken to establish the site of action in drug-induced hemiballismus. The present report describes the results of a large series of drug injections made systematically through indwelling cannulae aimed at the subthalamic nucleus, globus pallidus and surrounding structures in the conscious monkey. Some of the results of this study have been reported in abstract form (Crossman *et al.*, 1981).

METHODS

Experiments were performed on 10 adult monkeys of either sex (1 *Macaca mulatta*, 1 *Macaca irus* and 8 baboons—either *Papio cynocephalus* or *Papio anubis*). All surgical procedures were performed under general anaesthesia (ketamine hydrochloride and xylazine i.m.) taking aseptic precautions.

Stereotaxic Ventriculography

In early experiments stereotaxic coordinates for structures to be injected were taken directly from published stereotaxic atlases for the rhesus monkey (Snider and Lee, 1961), cynomolgus monkey (Shantha *et al.*, 1968) or baboon (Davis and Huffman, 1968). Experience showed that there was considerable variation in the precise location of intracerebral structures even between individuals of the same species, sex and weight. Stereotaxic ventriculography was therefore introduced in order to improve the accuracy of cannula placement. The anaesthetized animal was placed in a stereotaxic frame and radio-opaque contrast medium (Myodil, Glaxo; 1–2 ml) was introduced into the head or body of one lateral ventricle. Lateral radiographs were taken immediately following injection. The centre of the x-ray source lay in the stereotaxic horizontal zero plane and the axis of the beam was perpendicular to the sagittal plane. The source and the film cassettes were located 5.6 m and 15 cm lateral to the sagittal plane, respectively. A graduated radio-opaque reference scale was placed in the sagittal plane prior to the exposure of films. The films (fig. 1) were used particularly to locate the positions of the anterior and posterior commissures and to define the boundaries of the third ventricle. These were compared with standard atlases and an estimate made of any adjustment in stereotaxic coordinates which might be appropriate for deep intracerebral structures.

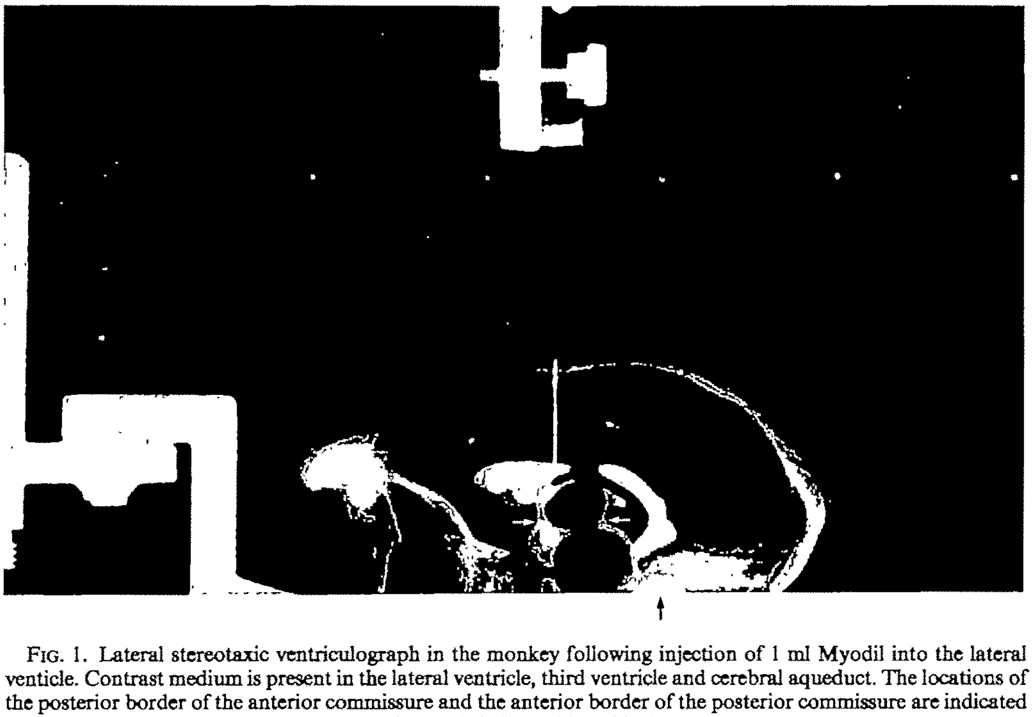

FIG. 1. Lateral stereotaxic ventriculograph in the monkey following injection of 1 ml Myodil into the lateral venticle. Contrast medium is present in the lateral ventricle, third ventricle and cerebral aqueduct. The locations of the posterior border of the anterior commissure and the anterior border of the posterior commissure are indicated by white arrows. Anteroposterior stereotaxic zero is indicated by a black arrow.

Implantation of Cannula Guides

Under general anaesthesia a stainless steel cannula guide was inserted into the brain under stereotaxic control and secured to the skull with self-tapping stainless steel screws and dental acrylic cement. The cannula guide consisted of a guide tube (0.46 mm o.d., 0.25 mm i.d.) attached to a base, the latter being located on the surface of the skull to serve as anchorage for the cement. The cannula guide was normally occupied by a blank which bore a stainess steel stylette (0.23 mm diameter) designed to maintain the patency of the guide tube. In early experiments removal of the blank permitted the freehand introduction of a stainless steel needle (0.20 mm diameter) attached to a Hamilton syringe through which intracerebral drug injections were made. In later experiments the cannula guide was modified to accept a mechanically operated micropump which was used for drug injection. The design and operation of this pump have been described in detail elsewhere (Needham *et al.*, 1983).

Intracerebral Drug Injections

Intracerebral drug injections (1.5–7 μl) were made in the conscious animal. Where injections were made using the micropump this was fitted in place under brief general anaesthesia (ketamine hydrochloride i.m.) at least 2 h before injection. Animals were observed for at least 1 h after injection, any apparent abnormalities of movement being noted and, where appropriate, recorded on film.

Substances injected were picrotoxin (Sigma) 3 μg/μl in sterile water, bicuculline methiodide (Pierce) 10 to 18 μg/μl in sterile saline, muscimol (Fluka) 1 μg/μl in sterile water, and sterile saline.

Confirmation of Injection Sites

At the end of the experiment animals were anaesthetized with ketamine hydrochloride i.m. and a lethal dose of barbiturate was then administered. Selected cannula tracks were marked with Indian ink at their deepest injection site. The animals were perfused transcardially with 0.9 per cent saline followed by 10 per cent neutral buffered formalin. Brains were blocked stereotaxically and frozen sections were prepared at 20 to 40 μm. Appropriate sections were stained with cresyl violet or Luxol fast blue and neutral red.

RESULTS

In 10 monkeys, injections were made at a total of 70 intracerebral sites located predominantly in the putamen, globus pallidus, subthalamus (including the subthalamic nucleus and zona incerta), internal capsule, cerebral peduncle and substantia nigra (figs. 2 and 3). Unambiguous abnormalities of movement were observed following injections at 22 of these sites. The most consistently observed abnormality was hyperkinetic activity of the limbs on one side of the body, having the features of hemichorea or hemiballismus, in response to injection of GABA antagonists into the contralateral subthalamic nucleus. Other forms of dyskinesia occurred after some injections in the immediate vicinity of the subthalamic nucleus or in the lateral pallidal segment or putamen.

Hemichorea and Hemiballismus

Nature of the dyskinesia. The diencephalic injection sites associated with contralateral limb hyperkinesia are detailed in the Table together with the pharmacological agent injected, the latency to onset of the disorder and its severity. Quantitative variations were seen in the limb hyperkinesia elicited from different subthalamic injection sites or in different animals. Qualitatively, however, the nature of the

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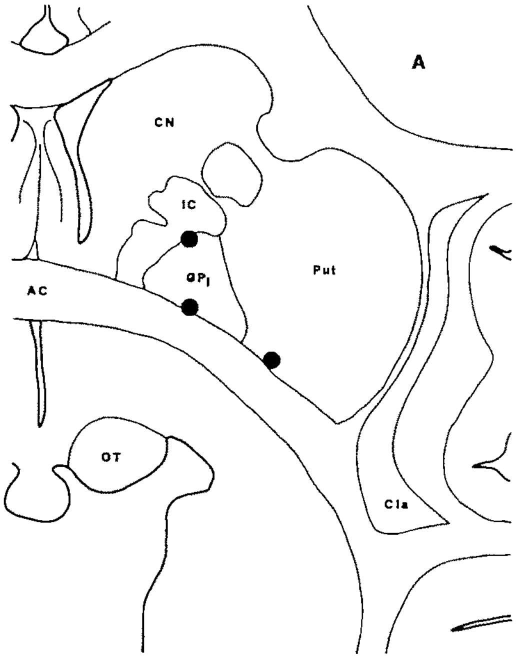
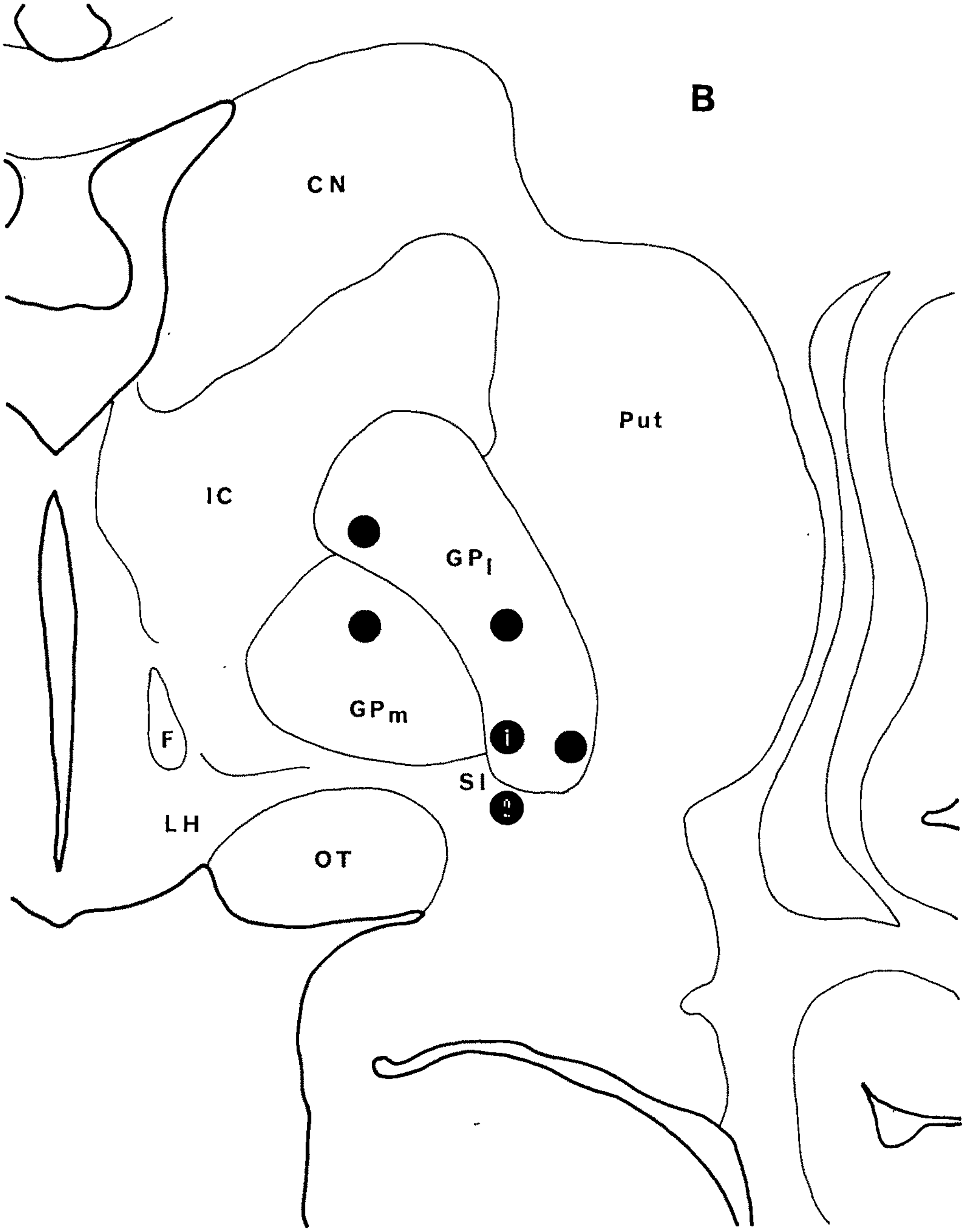


FIG. 2. A to I represent sections of the monkey brain taken parallel to the frontal zero plane and are based upon the atlas of Davis and Huffman (1968). Approximate stereotaxic levels in mm anterior to the interaural line are, for the baboon, A, 21.0; B, 18.0; C, 16.0; D, 14.0; E, 13.5; F, 13.0; G, 12.5; H, 10.0; I, 7.5. Black dots indicate the location of all intracerebral injection sites reported in the present study. Injection sites giving rise to any form of motor abnormality are individually identified (1–22). Those sites not individually identified did not give rise to any detectable form of motor abnormality when injected at least once with a dose of GABA antagonist at least sufficient to induce unambiguous limb dyskinesia when injected into the subthalamic nucleus. Injection sites are mapped with an anteroposterior accuracy of approximately 0.5 mm. Injection sites in the macaque are indicated with anatomical accuracy in the drawings but stereotaxic levels do not apply. In order to facilitate comparison and conserve space, all injection sites are represented on the right side. Of the 70 sites reported, 40 were on the right and 30 on the left.

ABBREVIATIONS

AC = anterior commissure
AV = nucleus anterior ventralis of thalamus
Cla = claustrum
CM = nucleus centrum medianum of thalamus
CN = caudate nucleus
CP = cerebral peduncle
DBC = decussation of the brachium conjunctivum
DG = dentate gyrus
F = fornix
FR = fasciculus retroflexus
GP$_l$ = globus pallidus, lateral segment
GP$_m$ = globus pallidus, medial segment
Hipp = hippocampus
IC = internal capsule
LD = nucleus lateralis dorsalis of thalamus
LGN = lateral geniculate nucleus
LH = lateral hypothalamus
MCP = middle cerebellar peduncle
MD = nucleus medialis dorsalis of thalamus
MGN = medial geniculat nucleus
ML = medial lemniscus
MM = medial mammillary nucleus
MTT = mammillothalamic tract
OT = optic tract
PG = parahippocampal gyrus
Pul = pulvinar
Put = putamen
R = nucleus reticularis of thalamus
RN = red nucleus
SI = substantia innominata
SM = stria medullaris
SN = substantia nigra
STN = subthalamic nucleus
VA = nucleus ventralis anterior of thalamus
VL$_m$ = nucleus ventralis lateralis of thalamus, pars medialis
VL$_o$ = nucleus ventralis lateralis of thalamus, pars oralis
VPL = nucleus ventralis posterior lateralis of thalamus
VPM = nucleus ventralis posterior medialis of thalamus
ZI = zona incerta
III = oculomotor nucleus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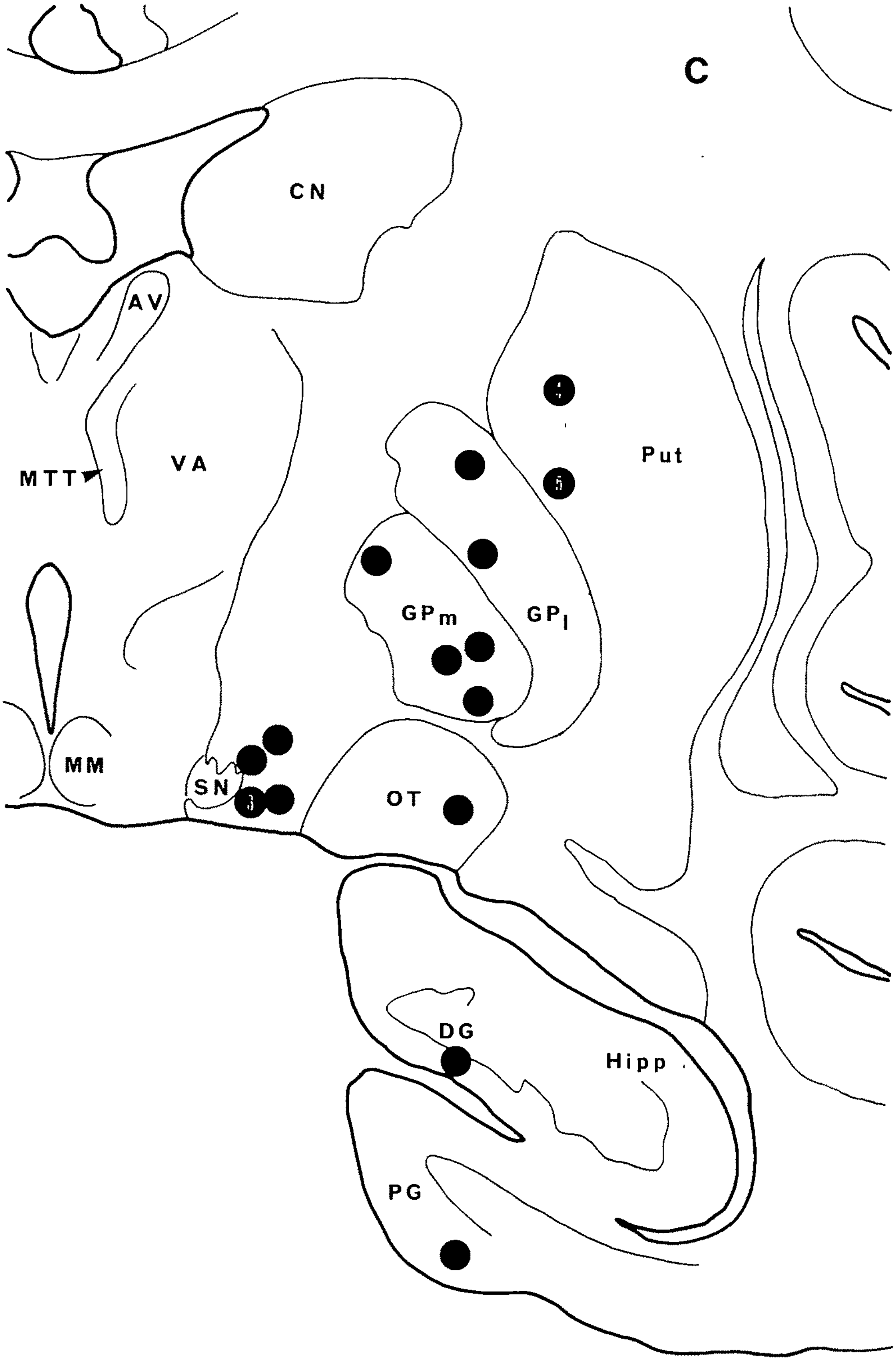
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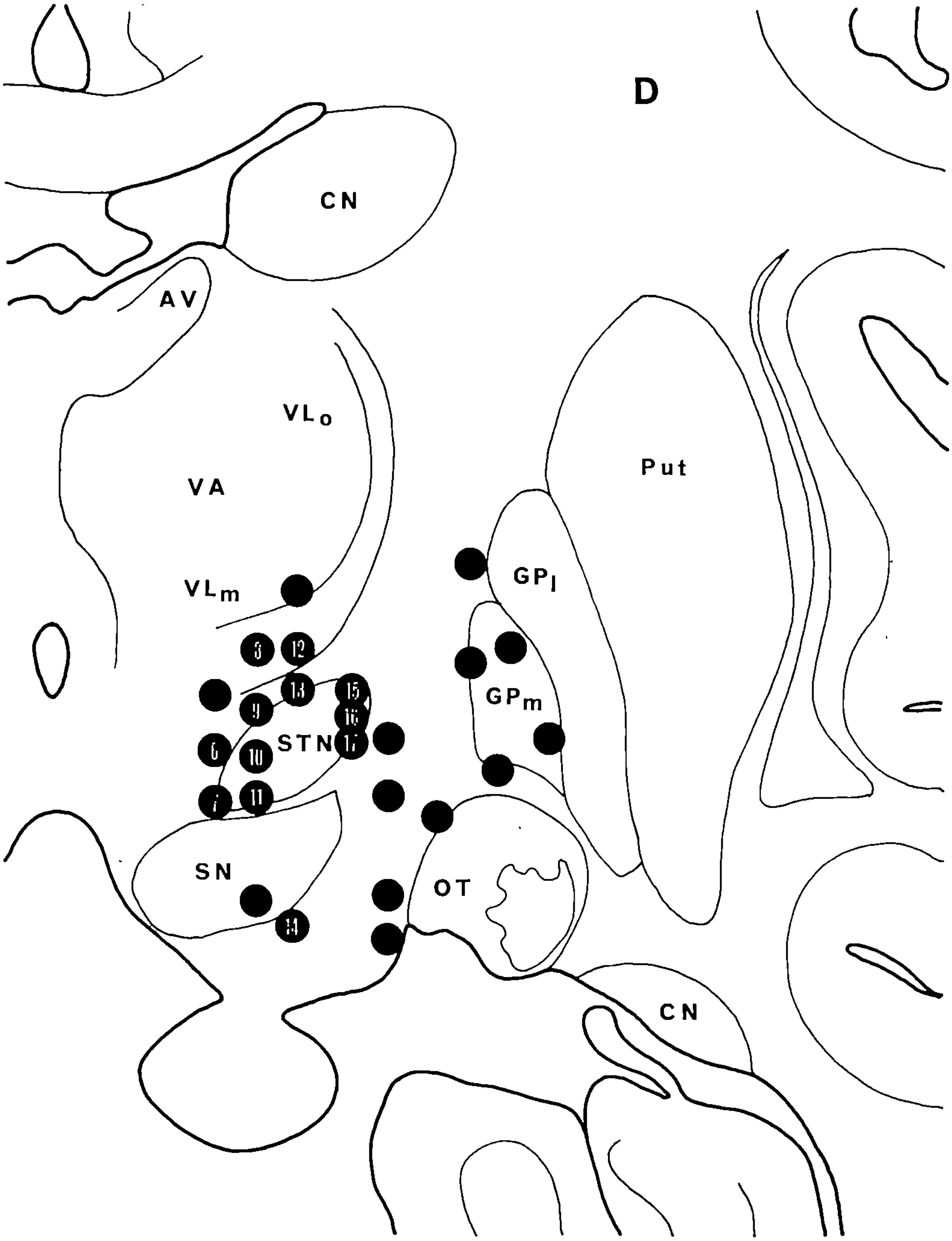
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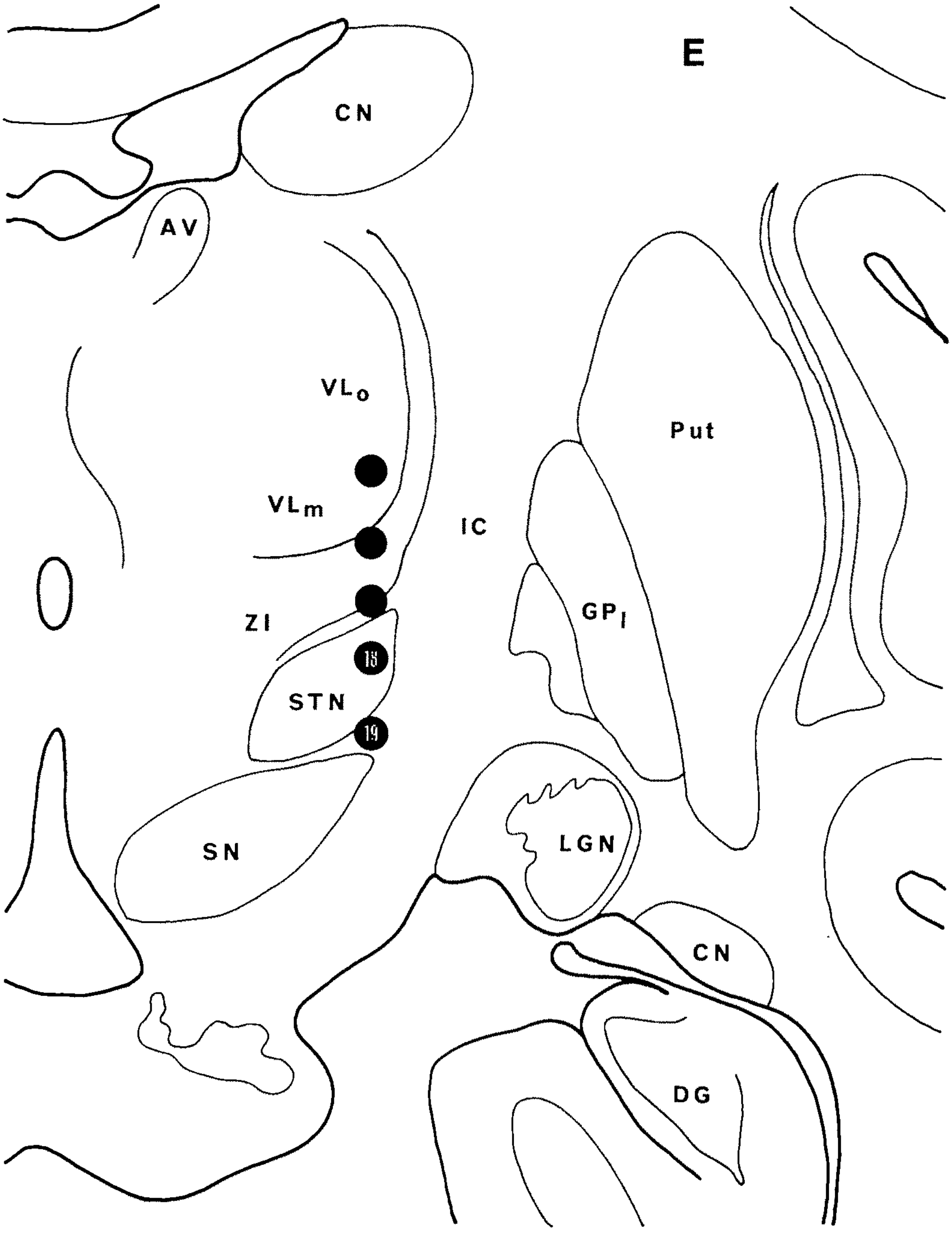
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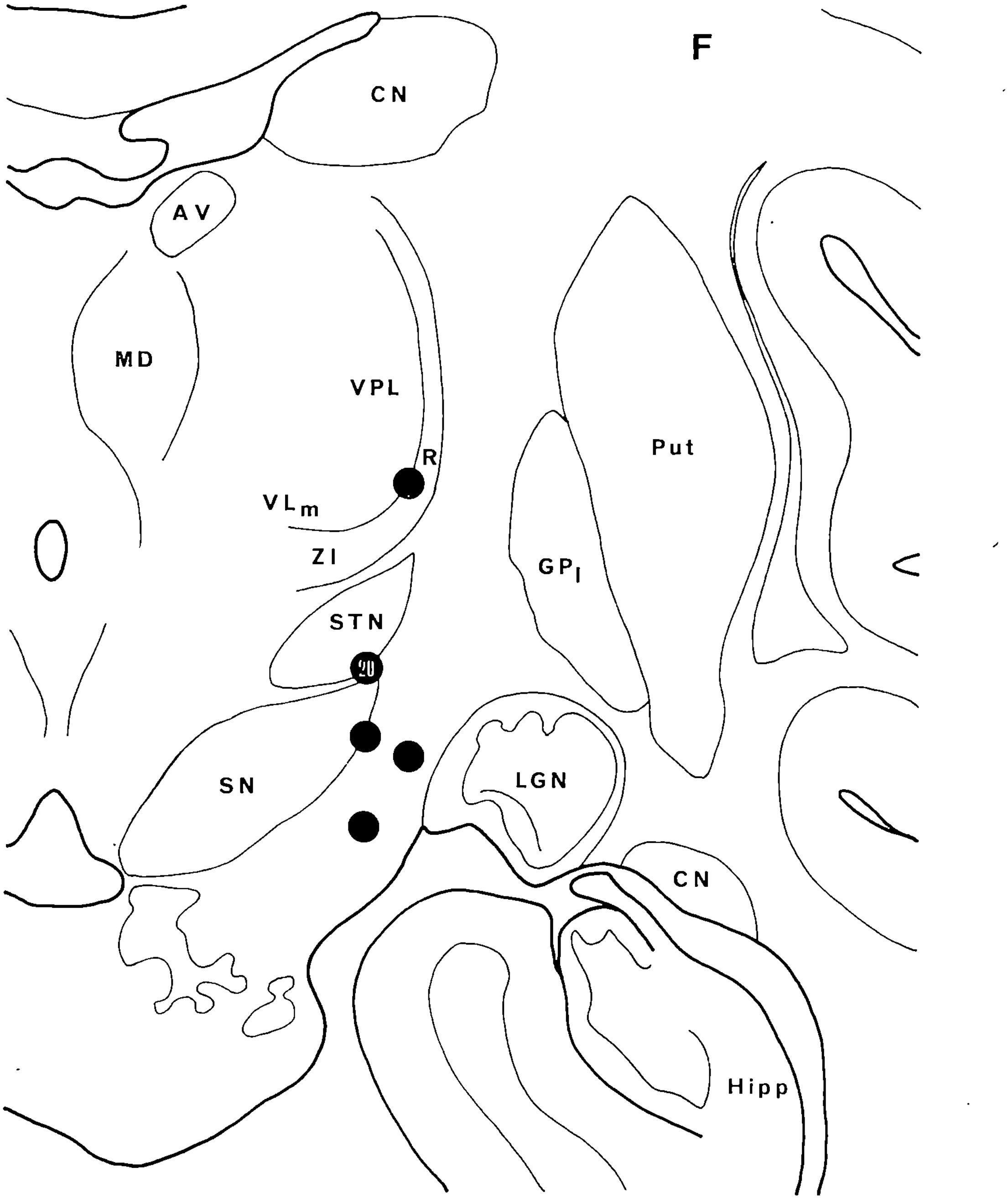
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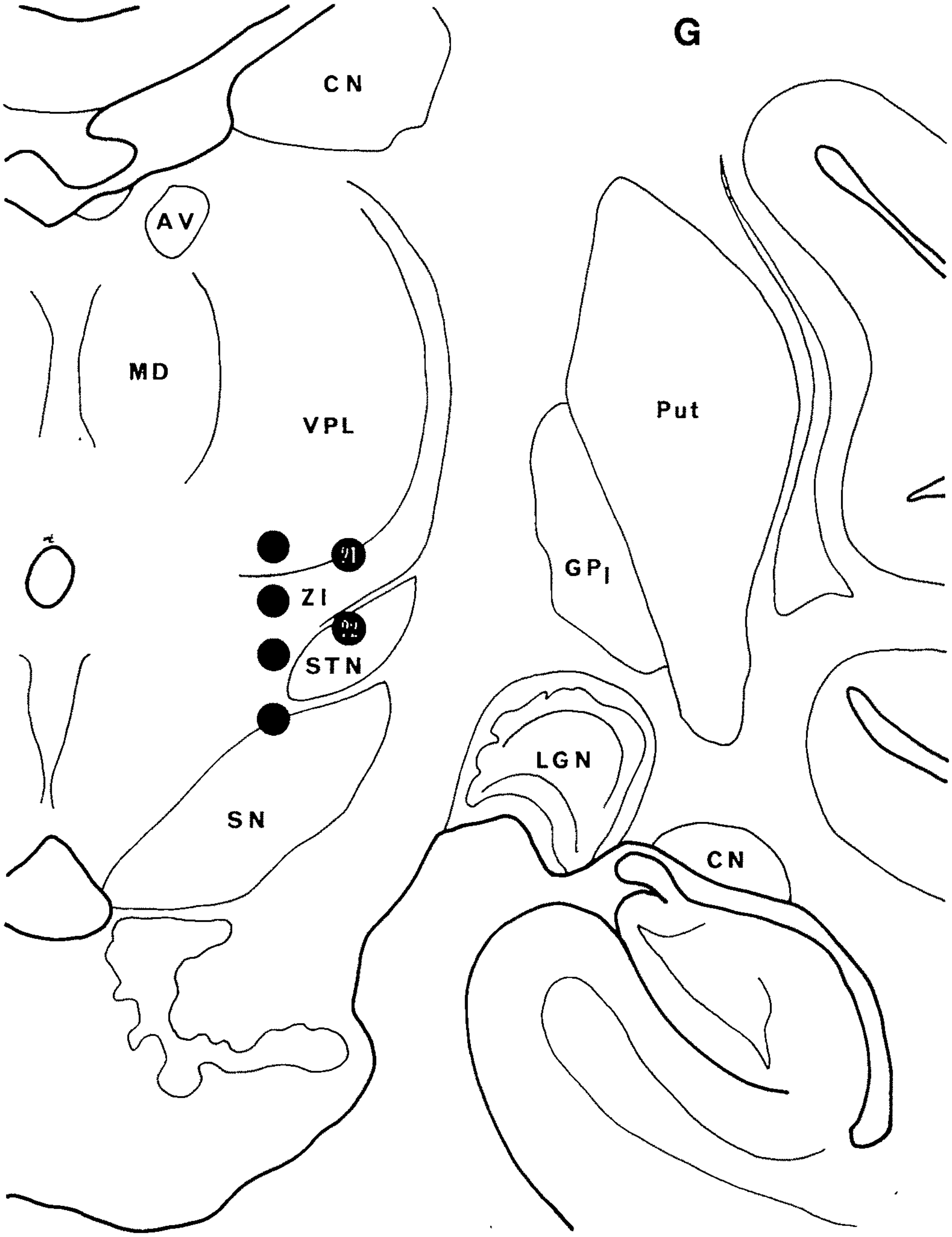
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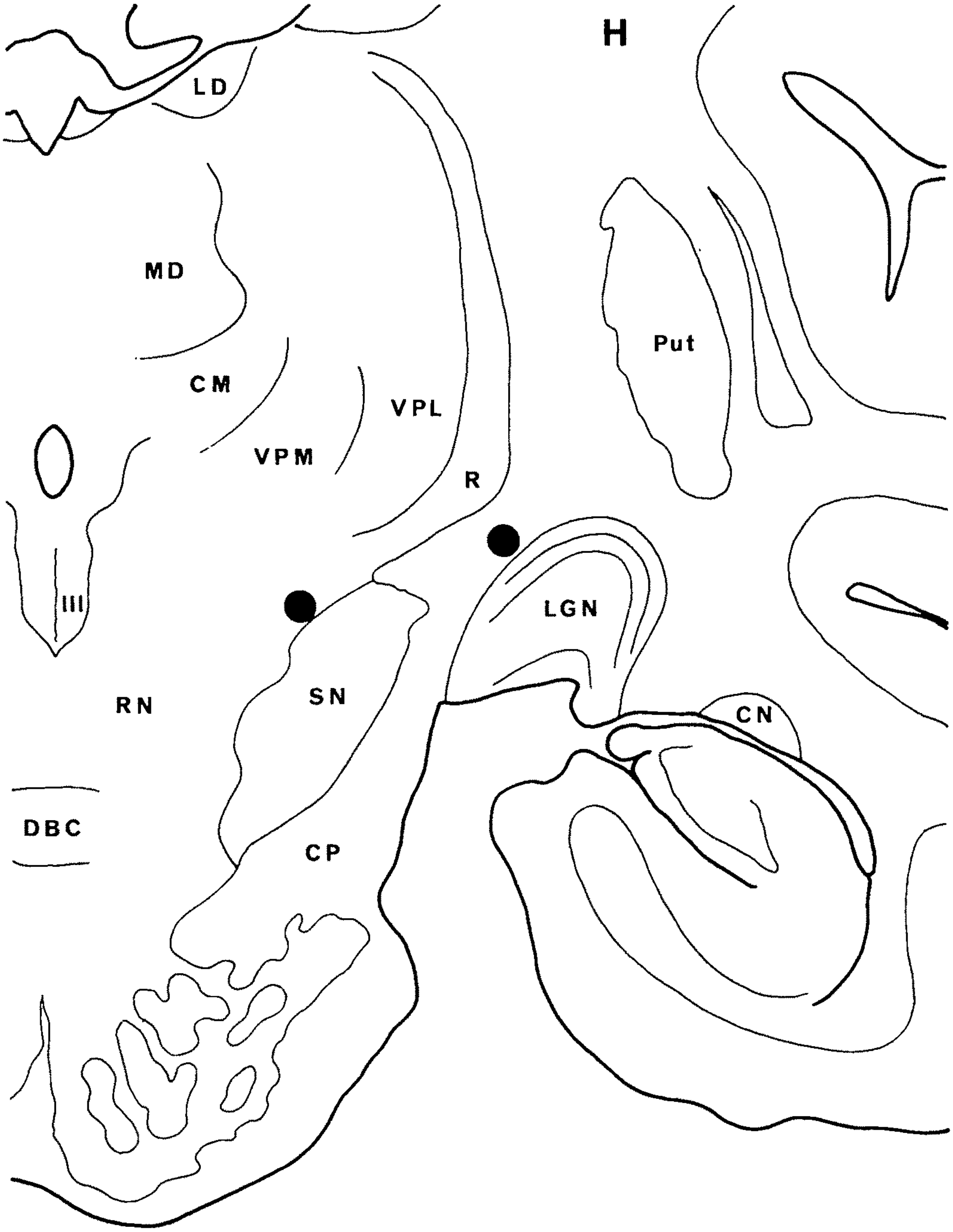
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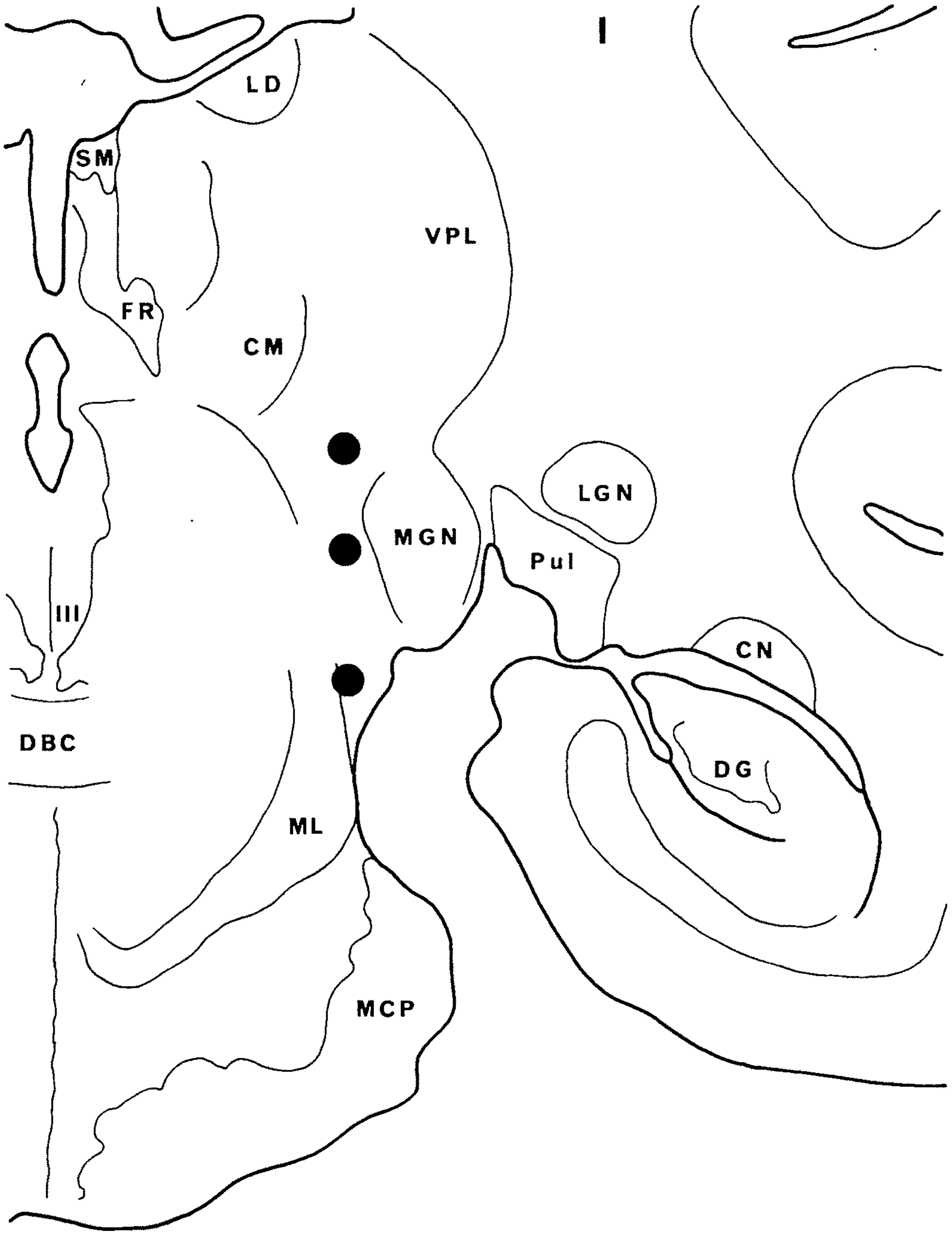
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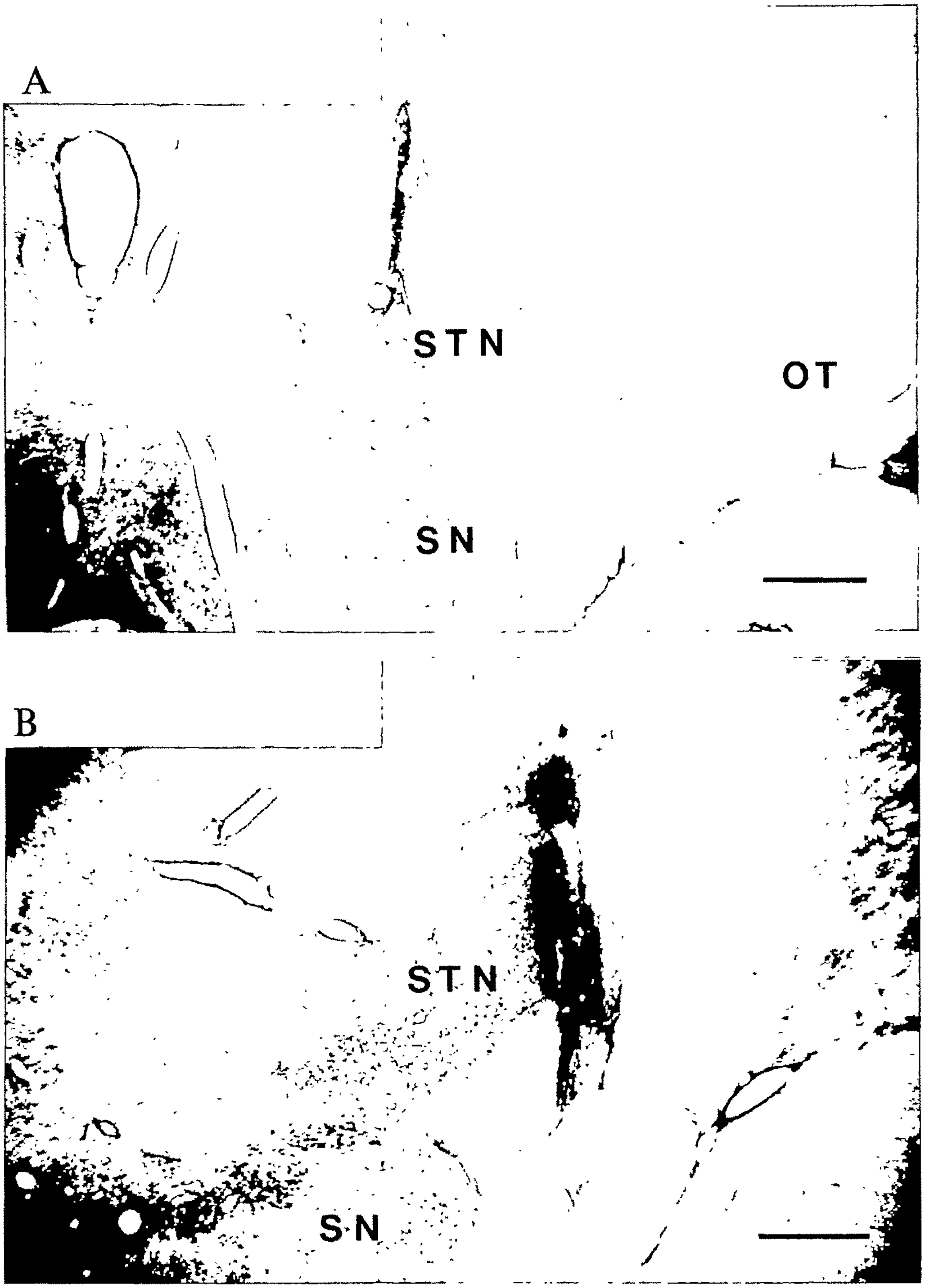

FIG. 3. Photomicrographs showing tracks stained with Indian ink, leading to subthalamic injection sites 9 (A) and 18 and 19 (B). Abbreviations as in fig. 2. Bars = 1 mm.

TABLE. SUMMARY OF DIENCEPHALIC INJECTION SITES GIVING RISE TO DYSKINESIA IN THE CONSCIOUS MONKEY

			Nature of limb dyskinesia					
			Upper limb		*Lower limb*			
Injection site code in fig. 2.	*Structure at injection centre*	*Pharmacological agent injected, dose and volume (No. of observations)*	*Severity* (— to + + +)	*Latency to onset (min)*	*Severity* (— to + + +)	*Latency to onset (min)*	*Torticollis severity* (— to + + +)	*Circling behaviour severity* (— to + + +)
3	Cerebral peduncle underlying rostral tip of substantia nigra	Bicuc., 30 μg in 2 μl (1)	+	125	—		+ +C	+ +C
6	Dorsomedial to subthalamic nucleus	Bicuc., 30 μg in 2 μl (1)	—		—		+ +	+ +
7	Ventromedial tip of subthalamic nucleus	Bicuc., 30 μg in 2 μl (1)	+	35	—		+ + +	+
8*	Zona incerta	Bicuc., 30 μg in 2 μl (1)	—		+	26	+	—
9*	Fasciculus lenticularis (H_2)	Bicuc., 30 μg in 2 μl (1)	—		+	125	+	+
10*	Subthalamic nucleus	Bicuc., 30 μg in 2 μl (1)	+	45	+	39	—	+
11	Subthalamic nucleus	Picro., 18 μg in 6 μl (2)	+ + +	25–31	+ + +	9–10	—	—
12	Zona incerta	Bicuc., 30 μg in 2 μl (1)	—		—		+ + +	+ + +‡
13	Fasciculus lenticularis (H_2)	Bicuc., 30 μg in 2 μl (1)	+	32	—		+ + +	+ + +‡
15	Subthalamic nucleus	Picro. 21 μg in 7 μl (1)	+ +	†	+ +	55	—	—
16	Subthalamic nucleus	Picro., 18 μg in 6 μl (2)	§	45	+ + +	30–33	—	—
17	Subthalamic nucleus/internal capsule	Picro., 18 μg in 6 μl (1)	+ + +	9	+ + +	9	—	—
		Bicuc., 10 μg in 1 μl (1)	—		+	45	—	—
		Bicuc., 30 μg in 2 μl (4)	+/+ + +	5–15	+/+ + +	5–15	—/+	—/+ +
		Muscimol, 2 μg in 2 μl (1)	—		—		—	—
18	Subthalamic nucleus	Bicuc., 30 μg in 2 μl (3)	+/+ +§	9–15	+	9–15	—	—
19	Ventral border of subthalamic nucleus	Bicuc., 30 μg in 2 μl (1)	+	20	+	30	—	+ +
20	Ventral border of subthalamic nucleus	Bicuc., 30 μg in 2 μl (1)	—		+	30	—	+
21	Thalamic fasciculus (H_1)	Bicuc., 30 μg in 2 μl (1)	+	11	+	11	—	—
22	Subthalamic nucleus	Bicuc., 30 μg in 2 μl (2)	+ + +	11	+ + +	6	—	+

The injection site code identifies the individual injection sites in fig. 2. The severity of limb dyskinesia was classified as either mild (+), moderate (+ +) or severe (+ + +) as defined in the text. Bicuc. = bicuculline methiodide. Picro. = picrotoxin. * Injections at these sites were accompanied by polydipsia. † Latency not known. ‡ Circling behaviour was accompanied by ataxia. § Abnormal arm movements were absent on one occasion following injections at both of these sites.

hyperkinesia was sufficiently similar between sites and between animals to permit description in a composite fashion.

Involvement of the upper limb was typically heralded by occasional fidgety movements which might at first be disregarded if it were not for their repetitive nature. Such movements were small in amplitude, relatively isolated, sudden in onset and rapidly executed. They affected all the major joints of the forelimb and consisted of abduction-adduction and flexion-extension of the shoulder, flexion-extension of the elbow, pronation-supination of the forearm and occasional extension of the wrist and fingers. Sometimes periods of slowly alternating flexion and extension of the wrist were noted. With the passage of time the severity of the disorder increased. The amplitude of the movements became greater and well-patterned movements about several joints began to occur in combination. For example, the limb would be stretched in front of the animal by flexion of the shoulder and extension of the elbow with the forearm pronated, then rapidly withdrawn, internally rotated and extended posteriorly. Rapid performance of these movements produced a sweeping action of the upper limb across the floor. In the most severe form of dyskinesia the upper limb exhibited virtually continuous abnormal movement. Uncontrolled flailing movements occurred either forwards, laterally or in a circumductive manner, not necessarily confined to a plane below shoulder level but sometimes extending above the head.

In the lower limb the most characteristic pattern of initial hyperkinesia was alternating flexion-extension of the ankle and abduction-adduction of the hip. When standing, the leg alternated between internal and external rotation about the hip, the heel acting as a pivot. With increasing severity, the leg was alternately extended and withdrawn with rapid forceful movements. Extension of the limb was associated with dorsiflexion of the ankle and extension of the toes, followed by flexion of the knee and a combination of flexion and internal rotation of the hip. The most extreme development of lower limb hyperkinesia was the appearance of rapid, wide circumductive movements of the whole leg which caused considerable ataxia. The animals sometimes used their unaffected limbs to limit the dyskinesia. The movements were temporarily exacerbated by excitement or disturbance.

For the purpose of written records the severity of the dyskinesia was judged by the amplitude and frequency of the involuntary movements. These ranged from localized movements which occasionally interrupted the animal's normal posture (mild), through more frequent, jerky, choreiform movements of moderate extent (moderate) to frank hemiballismus characterized by forceful movements of wide excursion (severe). The duration of the dyskinesia appeared to be between two and four hours. As a matter of course, however, animals were sedated or anaesthetized once the pattern of dyskinesia had become fully established. There invariably followed an uneventful recovery with no apparent after-effects.

Somatotopy. The extent and severity of involvement of the upper limb and lower limb were variable between different injection sites. Dyskinesia was sometimes confined entirely to the upper limb (sites 3, 7 and 13) or to the lower limb (sites 8, 9 and 20) but in the majority of cases both limbs were involved (sites 10, 11, 15–19, 21 and 22). Injections giving rise to dyskinesia in only one limb were generally located around the periphery of the subthalamic nucleus whereas injections well-placed within the nucleus commonly provoked dyskinesia in both contralateral limbs.

The latency to onset of unambiguous limb dyskinesia ranged from 5 to 125 min depending on the site of injection. The shortest latencies were generally associated with injection sites well-placed within the subthalamic nucleus. Considering all the diencephalic injection sites which gave rise to limb dyskinesia, the mean latency to onset of abnormal movements in the lower limb was less than that for the upper limb (mean latencies 24 min and 32 min, respectively). This was also the case taking into account only those injection sites which gave rise to severe dyskinesia classified as hemiballistic (mean latencies for lower and upper limbs 12 min and 20 min, respectively). At sites giving rise to dyskinesia classified as severe both limbs invariably became involved. Dyskinesia provoked in a single limb in isolation tended to be relatively mild in nature.

In view of the variability of limb involvement, careful analysis was made of data for each provocative injection site including the limb or limbs involved, the latency to onset and the severity of the dyskinesia, with the aim of clarifying the question of somatotopic organization within the subthalamic nucleus. No clear correlation could be established, however, between the latency to onset or severity of movement in a particular limb and the location of the provocative subthalamic site. Dyskinesia in the upper limb was elicited from sites throughout the anteroposterior, dorsoventral and mediolateral extents of the subthalamic nucleus. The most severe movements of shortest latency were obtained from sites in the lateral part of the subthalamic nucleus in the middle of its anteroposterior extent and also from the dorsal border of the posterior part of the nucleus. Similarly, lower limb dyskinesia was elicited from sites spread throughout the nucleus. Sites giving the most severe dyskinesia with shortest latency were situated ventrolaterally in the middle of the anteroposterior extent of the nucleus and dorsally in its posterior part. Except in the caudal part of the nucleus, dorsally and medially placed injections were less effective in provoking dyskinesia and had longer latencies to onset.

Involvement of orofacial musculature in the dyskinesia evoked by subthalamic injection of GABA antagonists was observed with only one site (22 in fig. 2) which was located in the caudal part of the subthalamic nucleus. The movements consisted of involuntary grimacing, involving predominantly the angle of the mouth, on the side ipsilateral to the hemiballismus.

Controls. These were performed for both the anatomical and pharmacological specificity of injections provoking dyskinesia.

Hemichorea or hemiballismus only occurred with injections into the subthalamic nucleus itself or into structures immediately adjacent. Moreover, hemichorea or hemiballismus was provoked from every injection site within the subthalamic nucleus itself. Injections made at more distant sites including the internal capsule, cerebral peduncle and globus pallidus were generally without effect upon motor activity (fig. 2). Injection sites within the subthalamic nucleus itself were associated with the shortest latencies to onset and the most severe form of dyskinesia. Longer latencies and less severe hyperkinesia were associated with injections on the periphery of the nucleus.

Control injections of substances other than GABA antagonists were made at a site selected for the reproducibility and severity of the dyskinesia which was induced by picrotoxin or bicuculline (site 17). During the early part of this study the GABA antagonist routinely employed was picrotoxin, injected in a volume of 6 μl vehicle. On two consecutive occasions injection of 6 μl saline at site 17 induced mild but unambiguous dyskinesia in both contralateral limbs. Not only was the dyskinesia mild in comparison to that induced by picrotoxin but its time course was quite different, the movements suddenly disappearing after 40 min at a time when picrotoxin-induced dyskinesia would typically be reaching its maximum intensity. Nonetheless, these observations highlighted the possibility of nonspecific or volume effects in the subthalamic nucleus and thereafter GABA antagonism was routinely achieved by injection of bicuculline methiodide in a volume of 2 μl vehicle. Injection of this volume of saline alone (2 μl) did not induce any form of detectable motor abnormality. As in a previous study (Crossman *et al.*, 1980) injection of the GABA agonist muscimol was without effect at a site where GABA antagonists induced severe dyskinesia. These observations are of considerable importance since negative effects of both saline (2 μl) and muscimol injection were preceded and followed at the same site by injections of bicuculline methiodide which induced marked dyskinesia in the contralateral limbs.

Torticollis and Circling

Torticollis and/or circling was observed after GABA antagonism (but only with bicuculline) at some of the sites associated with the development of hemichorea and hemiballismus (*see* Table). At two sites they occurred in the absence of limb dyskinesia. In all instances the torticollis was on a rostrocaudal axis with the face turned contralateral to the injected side. The severity of torticollis ranged from, at one extreme, occasional, irregular spasmodic turning of the head which was rapidly corrected, to, at the other extreme, a continual, maintained, dystonic posture of the head. Torticollis was often associated with apparent restlessness and generalized motor hyperkinesia, the most prominent component of which was compulsive ambulation in circles, the animal turning contralateral to the injected side. The tendency to circle ranged from occasional turning, which could have been easily disregarded if it was not for the consistency of its direction, to circling at up to 30 times per minute which was often associated with ataxia. The severity of torticollis was generally paralleled by the frequency of circling but on occasions a mild or moderate form of one existed alone.

Where torticollis and circling coexisted with hemichorea or hemiballismus their severity was not proportional to the severity of limb dyskinesia. Indeed, an almost reciprocal relationship appeared to exist between torticollis and circling and the severity of limb hyperkinesia (*see* Table). The most severe forms of either type of dyskinesia were found in isolation.

Other Forms of Dyskinesia

Injection of picrotoxin (12–18 μg in 4–6 μl, n = 4) at two sites near the ventral border of the lateral segment of the globus pallidus (sites 1 and 2, fig. 2) gave rise to an unequivocal hyperkinetic disorder of both contralateral limbs. In many respects the movements resembled the dyskinesia elicited by similar injections into the subthalamic nucleus but a marked difference was the presence of a prominent athetoid component in the movements of the upper limb. Abnormal involuntary movements began approximately 8 min after injection with periods of alternating flexion-extension of the wrist and abduction-adduction of the thumb. Approximately 10 min later there developed, in addition, alternating pronation-supination of the forearm and hand combined with continuous restless movements of the hand and digits which appeared athetoid in nature and were noted by several observers for their 'squirming' quality. Movements of the lower limb were characterized by alternating flexion-extension of the ankle and toes and by circumductive movements of the whole leg which occurred in combination with flexion-extension at the knee. The abnormal movements were exacerbated during periods of excitement or disturbance. There was no apparent interference with the ability to make voluntary movements and the animal was able to take food and eat using the affected upper limb.

Injection of picrotoxin (18 μg in 6 μl, n = 3) or bicuculline methiodide (22 μg in 1.5 μl, n = 2) into the dorsomedial putamen (sites 4 and 5, fig. 2) induced myoclonic, jerky movements of neck musculature and of the contralateral upper limb. The movements thus elicited were of a fairly fixed pattern and consisted of elevation of the abducted upper limb with the elbow flexed, synchronized with turning of the head towards the injected side. This sequence took approximately one or two seconds to perform and was repeated 10 to 15 times per minute. On one occasion myoclonic, twitching movements of the head and contralateral limbs were elicited by an injection located in the cerebral peduncle bordering on the ventral part of the substantia nigra (site 14).

DISCUSSION

The results of the present investigation confirm and extend the findings of our previous study (Crossman *et al.*, 1980) that unilateral limb dyskinesia, having the characteristics of hemiballismus or hemichorea, can be induced experimentally in the conscious monkey by injection of GABA antagonists into the contralateral subthalamic nucleus. To the best of our knowledge this constitutes the only model currently available where a truly human-like dyskinesia can be induced experimentally in the monkey by localized intracerebral drug injection.

Intracerebral Site of Action in Drug-induced Hemiballismus

One of the objectives of the present study was to identify the site of action of GABA antagonists in the production of experimental hemiballismus. In a previous communication in which ballistic activity following intracerebral drug injection was originally described (Crossman *et al.*, 1980) some doubt remained as to the site of action owing to the oblique placement of the injecting cannula such that drug injections into the subthalamic nucleus were made through the intervening globus pallidus and internal capsule. In the study presently reported, injections into the subthalamic nucleus were made by a vertical approach thus maintaining the integrity of the internal capsule. Some injections into the globus pallidus were made obliquely but never in such a way as to pierce the internal capsule.

Only injections into or very close to the subthalamic nucleus produced dyskinetic movements typical of hemiballismus. Moreover, the shortest latency to onset of movements, the most severe form of dyskinesia and the purest limb dyskinesia (without torticollis or circling) attended injections well-placed within the subthalamic nucleus. Injections into surrounding structures in general gave longer latency to onset of limb dyskinesia, limb dyskinesia complicated by torticollis and circling, or no dyskinesia at all. Injections into the medial segment of the globus pallidus never gave rise to observable dyskinesia. These observations leave little doubt that the site of action of GABA antagonists in producing hemiballismus in the present study was the subthalamic nucleus itself and that limb dyskinesia produced by injections centred in adjacent structures was due to diffusion of drug into the subthalamic nucleus.

This conclusion is as much unexpected as it is inescapable. Indeed, taking into account the known anatomical, electrophysiological, pharmacological and pathophysiological data on subthalamopallidal relationships, a site of action in the globus pallidus rather than the subthalamic nucleus might have been anticipated, for the following reasons. Heretofore, hemiballismus has usually been associated, both in man and in monkey, with destructive lesions involving the subthalamic nucleus (Whittier, 1947; Whittier and Mettler, 1949; Carpenter *et al.*, 1950). In addition, damage to the subthalamic fasciculus, which consists of subthalamopallidal and pallidosubthalamic fibres transversing the peduncular part of the internal capsule, has been considered to contribute to the development of dyskinesia attending experimental subthalamic lesions in the monkey (Carpenter *et al.*, 1950; Carpenter and Brittin, 1958). Since lesions involving the subthalamic nucleus and/or subthalamic fasciculus induce dyskinesia, while additional lesions involving the medial pallidal segment ameliorate the same dyskinesia (Carpenter *et al.*, 1950; Carpenter, 1961) it is reasonable to conclude that the major provocative element in lesions of the subthalamic fasciculus is involvement of subthalamopallidal fibres. There is evidence from studies in subprimate species that the subthalamopallidal projection is at least in part inhibitory upon globus pallidus neurons and that the neurotransmitter used by this pathway may be GABA (Larsen and Sutin, 1978;

Perkins and Stone, 1980; Nauta and Cuenod, 1982; Rouzaire-Dubois *et al.*, 1983). The production of dyskinesia by injection of GABA antagonists into the globus pallidus would, therefore, have been readily accommodated by current theories of subthalamopallidal relations in that blockade of GABA-mediated subthalamopallidal transmission in the globus pallidus might mimic the effect of subthalamic nucleus lesions leading to abnormal discharge of pallidal neurons.

This theory remains an attractive one despite the negative effects of pallidal injections in the present study. The primate pallidum is a large structure and subthalamopallidal terminals are widespread (Nauta and Cole, 1978; Carpenter *et al.*, 1981). The single site injections made in the present study can therefore only have involved a relatively small proportion of the pallidum by diffusion. Indeed, it would be predicted that dyskinesia resembling that produced by subthalamic nucleus lesions could be reproduced by effective and widespread blockade of subthalamopallidal synaptic transmission using appropriate techniques.

The subthalamic nucleus itself is also probably a site of GABA-mediated transmission—especially from inhibitory pallidosubthalamic fibres originating in the lateral pallidal segment (Tsubokawa and Sutin, 1972; Fonnum *et al.*, 1978; Rouzaire-Dubois *et al.*, 1980; Vincent *et al.*, 1982; *but see also* Van der Kooy *et al.*, 1981). The relationship, if any, of this pathway to the production of hemiballismus in the present study remains speculative. The precise mechanism in operation in terms of subthalamic and pallidal neuronal activity during hemiballismus will be the subject of further experimental studies.

Relationship of Drug-induced Dyskinesia to Dyskinesia Caused by Subthalamic Nucleus Lesion

An important consideration is the relationship between the form of dyskinesia observed in the present study following injection of GABA antagonists into the subthalamic nucleus and the form of dyskinesia observed in the monkey following subthalamic nucleus lesions. The major source of data on the latter is found in the extensive and carefully documented work of Carpenter and collaborators (Whittier and Mettler, 1949; Carpenter *et al.*, 1950; Carpenter and Carpenter, 1951; Carpenter and Mettler, 1951). Comparison of written records shows that although the mode of onset and the duration of dyskinesia were quite different in the two types of study—due to the different provocative technique—nevertheless the nature of the dyskinesia itself appears to have been very similar, with one or two reservations. Of particular significance is the choreic nature of the movements when present in a mild or moderate form in both types of study. When severe the movements resembled those of hemiballismus in man. Furthermore, comparison of film records showed that the movements elicited by intracerebral drug injection in the present study were typical of subthalamic dyskinesia produced by subthalamic nucleus lesions in the monkey (M. B. Carpenter, personal communication).

Following subthalamic lesions the lower limb was more commonly involved in dyskinesia than the upper limb. Indeed, while the lower limb might be involved in unequivocal abnormal activity in isolation, the arm never was (Whittier and Mettler, 1949; Carpenter *et al.*, 1950; Carpenter and Carpenter, 1951). A significant finding of the present study, therefore, was that unambiguous dyskinesia was observed on a number of occasions in the upper limb alone (sites 3, 8 and 13). It may be noted, however, that none of these injection sites was well-placed in the subthalamic nucleus and on each occasion the abnormality was mild. Severe dyskinesia in the upper limb was always preceded by the appearance of abnormal movement in the lower limb. Thus, in agreement with previous lesion studies, it appears that in the monkey, subthalamic dyskinesia is more readily and easily provoked in the lower than the upper limb.

The observation of dyskinesia in the upper or lower limb in isolation, whether or not followed by involvement of the other limb, is important. It speaks most strongly in support of the existence of somatotopic organization within the subthalamic nucleus. Unfortunately, the details of this somatotopy remain elusive (*see also* Carpenter and Carpenter, 1951). It was not possible to obtain supportive evidence for the somatotopic plan implied by recent anatomical and electrophysiological studies (Hartmann-von Monakow *et al.*, 1978; DeLong and Georgopoulos, 1979). In experimental lesion studies, dyskinetic involvement of facial, glossal or deglutitional muscles was never found (Carpenter and Carpenter, 1951), whereas in the present study abnormal facial movements were noted with only one injection site (site 22) located in the caudal part of the subthalamic nucleus. It is ironic, therefore, that the only plausible evidence of somatotopy from human pathological studies (Carpenter and Carpenter, 1951) suggests that lesions of the oral pole of the nucleus may be associated with facial dyskinesia.

While it is beyond the scope of this discussion to consider in detail the relationship between chorea and ballism, the present findings emphasize the esential similarities between these conditions as provoked experimentally in the monkey. In particular it is worthwhile to note that individual injections of GABA antagonists at particular subthalamic sites often provoked dyskinesia which was initially mild or moderate, having the characteristics of chorea, becoming frankly hemiballistic with the passage of time. This was interpreted as due to a progressive increase in effectiveness of drug action within the subthalamic nucleus.

Other Forms of Dyskinesia

The appearance and severity of torticollis and circling behaviour was negatively correlated with the presence and severity of limb dyskinesia. This suggests that the anatomical substrate subserving these forms of motor abnormality are different. The most severe torticollis and circling were obtained from injections located dorsal to the subthalamic nucleus in or near the zona incerta. Head turning, postural asymmetry and circling are rather ubiquitous findings with unilateral brain lesions or stimulation. Their occasional involvement in the syndrome elicited by injection into the subthalamic nucleus appears to have been incidental and not primarily related to the subthalamic nucleus itself.

The production of abnormal movements having an athetoid quality from sites near the ventral border of the lateral pallidal segment highlights the possibility of producing primate models of other human-like dyskinesias by localized pharmacological action in the basal ganglia and certainly deserves further attention in future studies.

ACKNOWLEDGEMENTS

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LIPID ABNORMALITIES OF XANTHOMATOUS NERVES

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SUMMARY

The lipid composition of nerves, with and without xanthomatous alteration, and other tissues, was investigated post-mortem in a 36-year-old man with cholestatic hepatitis of unknown cause and insulin-dependent diabetes mellitus (IDDM). Cholesteryl esters were found to be markedly increased in both endoneurium and epi- and perineurium of hepatic nerves (showing xanthomatous change), but not in sciatic nerve (without this change). Cholesteryl ester concentrations were also increased, but to a lesser degree, in kidney tissue. The fatty acid composition of stored cholesteryl esters in hepatic nerve endoneurium revealed that oleic acid was the most favoured substrate for esterification. A widespread depletion of triacylglycerol was also demonstrated in hepatic and sciatic nerves and liver and skin tissues obtained from this patient. This abnormality did not appear to be due to an alcoholic or biliary cirrhosis, or to inanition. Whether the depletion of triacylglycerol is drug-related or represents an endogenous metabolic error remains unclear.

INTRODUCTION

Lipid metabolism may be altered in primary biliary cirrhosis (Sherlock, 1968). A relationship between the elevated plasma cholesterol level and cutaneous xanthomata has been suggested (Ahrens *et al.*, 1950). An association between elevated plasma cholesterol and nerve pathology came from a study of three patients with biliary cirrhosis and mild hyperalgesic neuropathy characterized by 'painful paresthesia' of the fingers and hands (Thomas and Walker, 1965). These authors found excessive amounts of lipid, identified by histochemical criteria as cholesterol, in large distended cells especially in the perineurium. Characterization of the lipids related to this xanthomatous neuropathological change has not been reported. The patient whose nerve lipids are reported here had insulin-dependent diabetes mellitus since childhood and chronic, possibly drug-induced cholestatic hepatitis from which he died. Xanthomatous neuropathy of hepatic nerves was recognized only at post-mortem examination. Limb nerves did not show this change (Ludwig *et al.*, 1982). We have investigated the lipid composition of hepatic nerves showing xanthomatous change and limb nerves without xanthomatous change and have compared these to the same nerves from four disease control groups. The patients of the first group died suddenly from automobile accidents or heart attacks (sudden death group), the second group from biliary cirrhosis, the third group from alcoholic cirrhosis and the fourth group after severe inanition due to neoplastic disease. By comparing these groups, it was hoped that some inferences could be made about the association between lipid composition and histological change and disease. Unfortunately, in the case of our patient, plasma lipid studies had not been performed prior to death.

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MATERIALS AND METHODS

Autopsy samples of hepatic and sciatic nerves, liver, lung, kidney, spinal cord, frontal lobe, cerebellum, skin, fat, thyroid and adrenal gland (all fixed in formalin) and haemolysed blood were obtained from our patient with xanthomatous neuropathy. The clinical features and laboratory results have already been reported (Ludwig *et al.*, 1982). To ascertain whether the metabolic abnormality which was found might be related to biliary cirrhosis, cachexia, or diabetes mellitus, similar tissue was obtained from patients dying suddenly (4), with alcoholic cirrhosis (3), biliary cirrhosis (6), diabetic neuropathy (2) and cachexia from neoplastic disease (2).

Fat and adjacent tissue were removed from hepatic and sciatic nerves and the endoneurium was separated from the epineurial and perineurial tissue on a cold plate (surface temperature, 10° C) under a dissecting microscope. Subcutaneous fat and hair were removed from skin samples. All specimens were rinsed three times with normal saline and blotted dry with filter paper to remove as much formalin as possible.

About 10 to 30 mg of hepatic endoneurium (or epi- and perineurium), 50 mg of sciatic endoneurium (or epi- and perineurium), or 100 mg of the tissue samples were homogenized with 9 ml of $CHCl_3$-CH_3OH (2:1, v/v) employing a Polytron tissue homogenizer (Brinkman, Des Plaines, IL) and filtered into a separator funnel. The residue was re-extracted with another 9 ml of $CHCl_3$-CH_3OH (2:1, v/v) followed by successive re-extractions of the filtrates with 15 ml of $CHCl_3$-CH_3OH (1:1, v/v) and 30 ml of $CHCl_3$-CH_3OH (1:2, v/v) plus 8 ml of 2 M KCl. The final extract was filtered into the separator funnel and mixed with 37.5 ml $CHCl_3$ and 12 ml H_2O. Haemolyzed blood (5 ml) was added in drops to 20 ml CH_3OH on a magnetic stirring plate; 40 ml $CHCl_3$ was added and stirring continued for 2 h at room temperature. The residue was re-extracted with 30 ml $CHCl_3$-CH_3OH (2:1, v/v) for 2 h with gentle heating, and 20 ml 0.1 M KCl mixed thoroughly with the combined extracts. The layers of all extractions were allowed to separate overnight in a cold room (4°C) and the lower phase was evaporated to dryness in a rotary evaporator. The residue was suspended in a small amount of chloroform for further analysis.

Aliquots from the total lipid sample were separated into total phospholipids, free cholesterol, free fatty acid, triacylglycerols and cholesteryl esters by high performance thin-layer chromatography (HPTLC) (Whatman, Clifton, NJ) using hexane: diethyl ether: acetic acid (75:23:2, by volume) as developing solvent system. Total phospholipids were further separated into their subclasses by HPTLC using methyl acetate: n-propanol: chloroform: methanol: 0.25 per cent KCl (25:25:25:10:9, by volume) as the developing solvent system (Vitiello and Zanetta, 1978). When cholesteryl esters were recovered for methylation, a silica gel G plate (Analtech, Newark, DE) was used. The cholesteryl esters were transesterified by sodium methoxide reagent (Luddy *et al.*, 1960). The resulting methyl esters were further purified by TLC using petroleum ether: diethyl ether: acetic acid (90:10:1, by volume) as developing solvent system (Metcalfe *et al.*, 1966). All methylated fractions were analysed on a Packard Gas Chromatograph (GC), Model 419 (Downers Grove, IL) equipped with hydrogen detectors. The operating conditions for GC were as described previously (Yao *et al.*, 1976).

Quantitative analysis of total phospholipids, free cholesterol, free fatty acids, triacylglycerols and cholesteryl esters was carried out by a liquid scintillation counting procedure (Shand and Noble, 1980). The plate was charred at 180° C for 15 min after spraying with 3 per cent (w/v) cupric acetate in 8 per cent (w/v) phosphoric acid (Fewster *et al.*, 1969). The charred bands were scraped off into scintillation vials and suspended in 4 ml of distilled water. After addition of 10 ml of Ready-Solv MP (Beckman, Irvine, CA) scintillation cocktail, the vials were shaken vigorously to trap the charred lipids in the resultant firm gel. The amount of quenching due to the presence of the charred lipids was then measured by counting each sample for 5 min in the external standard channel ratio (ESCR) mode of the liquid scintillation counter (Model LS-333, Beckman, Fullerton, CA). The relationship between the ESCR and the mass of the lipid was linear up to at least 50 μg.

RESULTS

To recognize the effect of formalin fixation on nerve lipids, we compared the HPTLC profile of endoneurial lipids in fresh and fixed tissues (fig. 1). No lipid breakdown products were recognized in fixed as compared with fresh tissue.

A large amount of cholesteryl ester had accumulated in the hepatic nerve endoneurium (fig. 1) of our patient. A similar accumulation was also demonstrated in the epi- and perineurial fraction (fig. 2). No such accumulation was found for endoneurium (data not shown) or epi- and perineurium of sciatic nerve (fig. 3).

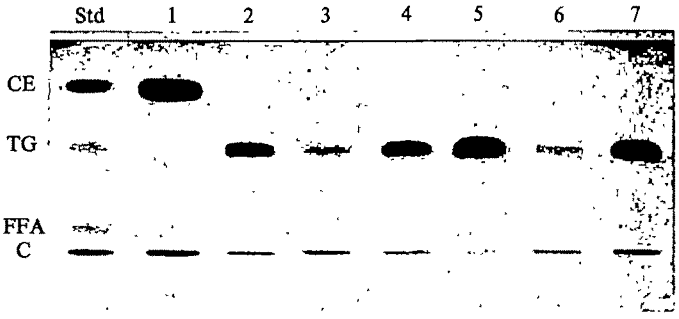

FIG. 1. High performance thin-layer chromatogram of nonpolar lipid profile of human hepatic endoneurium. CE = cholesteryl ester; TG = triacylglycerol; FFA = free fatty acid; C = cholesterol; Std = standard; 1 = patient; 2–4 = control nerves with 10 per cent formalin fixation; 5–7 = control nerves from 2–4 without fixation. Each sample represents nonpolar lipids obtained from 0.2 mg (dry weight) of hepatic endoneurium.

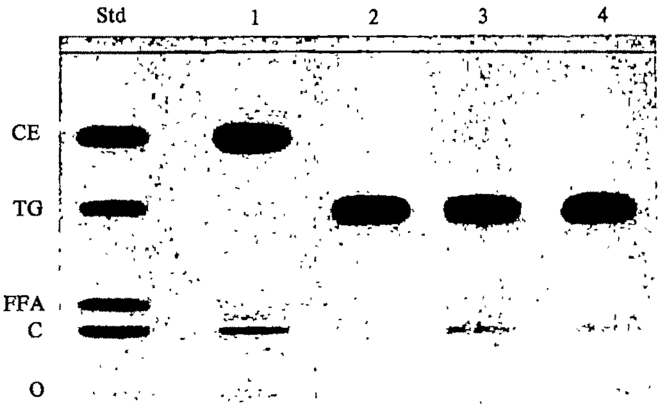

FIG. 2. High performance thin-layer chromatogram of nonpolar lipid profile of human hepatic epi- and perineurium. O = origin; 1 = patient and 2–4 = control nerves with 10 per cent formalin fixation. For explanation of other abbreviations, *see* fig. 1. Each sample represents nonpolar lipids obtained from 0.2 mg (dry weight) of epi- and perineurium.

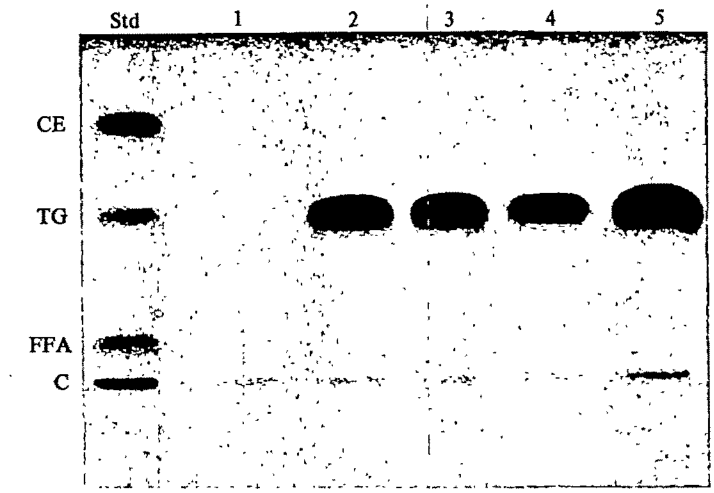

FIG. 3. High performance thin-layer chromatogram of lipid profile of fixed sciatic epi- and perineurium. 1 = xanthomatous neuropathy; 2 = normal; 3, 4 = diabetic neuropathy and 5 = primary biliary cirrhosis. For explanation of other abbreviations, *see* fig. 1. Each sample represents lipid contents obtained from 2 mg (wet weight) of epi- and perineurium.

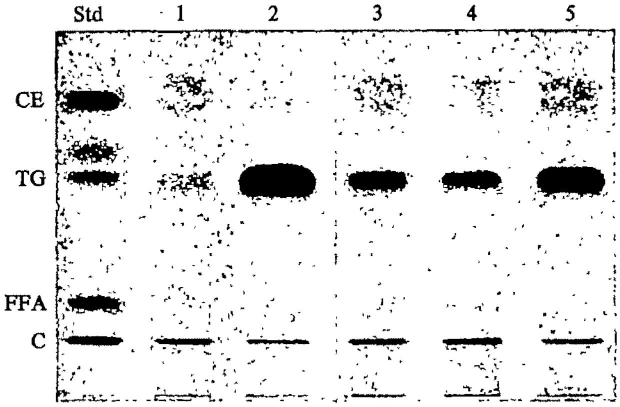

FIG. 4. High performance thin-layer chromatogram of nonpolar lipid profile from fixed human skin tissue. 1 = xanthomatous neuropathy; 2 = normal; 3, 4 = patients with cachexia and 5 = primary biliary cirrhosis. For explanation of abbreviations, *see* fig. 1. Each sample represents lipid contents obtained from 3 mg of wet weight of skin tissue.

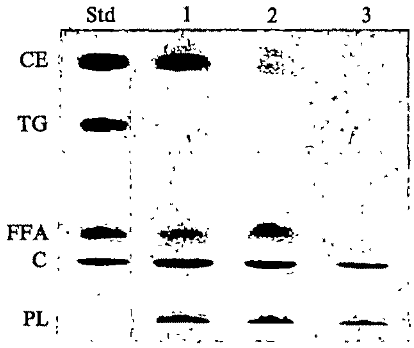

FIG. 5. High performance thin-layer chromatogram of nonpolar lipid profile from human kidney. PL = phospholipid; 1 = xanthomatous neuropathy; 2, 3 = controls. For explanation of other abbreviations, *see* fig. 1. Each sample represents lipid contents obtained from 5 mg (wet weight) of kidney tissue.

On the other hand, a deficiency of triacylglycerol was demonstrated for both hepatic nerve (figs. 1 and 2) and sciatic epi- and perineurium (fig. 3). A substantial decrease of triacylglycerol was also found in skin tissue obtained from our patient (fig. 4). This type of triacylglycerol reduction was not demonstrated in either sciatic nerve or skin tissue obtained from patients with primary biliary cirrhosis, diabetic neuropathy or cachexia (figs. 3 and 4).

Lipid profiles of cerebellum, frontal lobe, adrenal, thyroid, spinal cord and lung were also examined. No abnormalities were detected. However, a modest increase of cholesteryl esters was observed in the patient's kidney (fig. 5). This was not as great as in the hepatic nerves (figs. 1 and 2). The lipid profile of liver samples was also investigated using HPTLC. Unfortunately, many degradative products, particularly free fatty acids, were revealed due to formalin fixation (fig. 6). Interpretation of the results was, therefore, difficult. Nevertheless, a deficiency of triacylglycerol was again demonstrated.

The lipid profile of haemolysed blood from our patient was compared with control blood with and without haemolysis (fig. 7). The triacylglycerol concentration

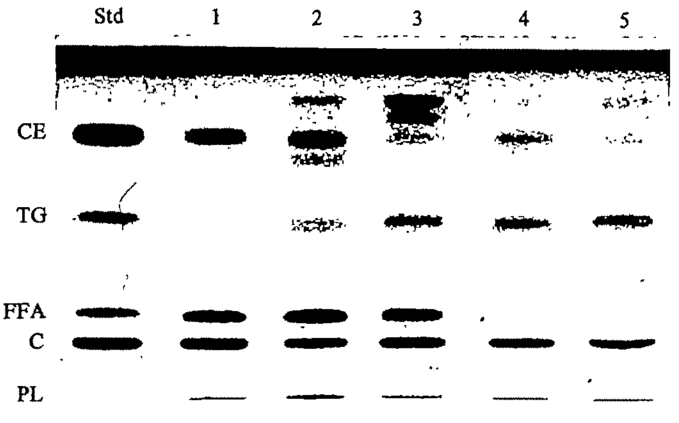

FIG. 6. High performance thin-layer chromatogram of lipid profile of human liver. 1 = fixed tissue from xanthomatous neuropathy; 2, 3 = fixed tissue (10 per cent formalin) from controls and 4, 5 = nonfixed tissue from controls. For explanation of abbreviations, *see* figs. 1 and 5. Each sample represents lipid contents obtained from 3 mg (wet weight) of liver.

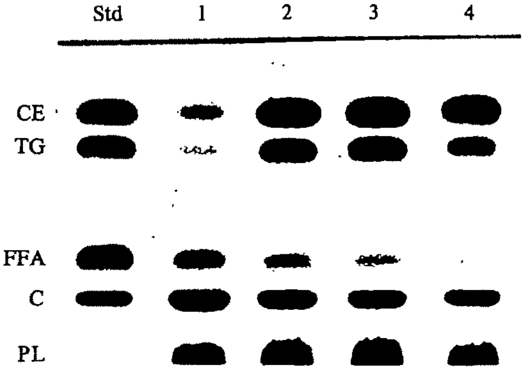

FIG. 7. High performance thin-layer chromatogram of total lipid profile of human blood. 1, 2, 3 = haemolysed blood from patients with xanthomatous neuropathy, with cirrhosis and control, respectively, 4 = nonhaemolysed blood from normal control. For explanation of abbreviations, *see* figs. 1 and 5. Each sample represents 0.03 ml of blood lipids.

was lower in the patient's plasma than in control subjects. An increased free fatty acid concentration in the patient's blood was apparently due to haemolysis. In addition, the percentage of esterified cholesterol to total cholesterol was markedly reduced in the patient's blood. Plasma samples obtained from three of the patient's immediate relatives were also analysed. No lipid abnormalities were found.

The fatty acid composition of cholesteryl ester from hepatic endoneurium is shown in the Table. The proportions of 16:0, 16:1 and 18:0 were markedly lower while that of 18:1 was more than twice as high in the patient than in control samples with or without fixation.

TABLE. FATTY ACID COMPOSITION (PER CENT) OF CHOLESTERYL ESTER FROM HUMAN HEPATIC ENDONEURIUM

	Patient	*Controls*	
Fatty acids	*Fixed*	*Fixed (3)*	*Fresh (3)*
14:0	—	0.7 ± 0.3	3.4 ± 0.2
15:0	—	0.5 ± 0.2	2.8 ± 0.4
16:0	15.5	33.2 ± 7.0	25.7 ± 1.3
16:1	3.9	6.2 ± 3.3	14.7 ± 1.2
18:0	2.9	16.4 ± 2.0	10.0 ± 0.5
18:1	50.8	18.5 ± 0.8	23.9 ± 4.0
18:2	12.1	9.2 ± 3.0	10.4 ± 0.5
20:0	—	1.4 ± 0.2	1.1 ± 0.2
20:1+18:3	1.1	0.8 ± 0.2	0.6 ± 0.3
20:2	1.1	—	0.2 ± 0.1
20:3+22:0	2.2	1.7 ± 0.5	0.5 ± 0.1
20:4+22:1	4.8	1.4 ± 0.3	0.3 ± 0.1
22:4+24:1	3.4	1.4 ± 0.4	0.4 ± 0.1
24:0	0.2	2.5 ± 0.8	1.0 ± 0.1

The sum is less than 100 per cent in each case because some minor and unidentified acids were omitted from the final tabulation.

DISCUSSION

Xanthomatous neuropathy is a rare complication of biliary cirrhosis, possibly related to the deposition of lipid in peripheral nerves (Thomas and Walker, 1965). We (Ludwig *et al.*, 1982) have reported a fourth case of xanthomatous neuropathy in which the patient did not have primary biliary cirrhosis. We have now demonstrated that cholesteryl esters are strikingly increased in nerves (both in endoneurium and epi- and perineurium) showing the xanthomatous change (hepatic nerve) but not in those without it (sciatic nerve). An increase of cholesteryl esters in kidney tissue was also found. These results correlate well with previous histological and morphological findings demonstrating the accumulation of sudanophilic lipids in the patient's hepatic nerve (Ludwig *et al.*, 1982).

In experimental xanthoma tissues, Kodama *et al.* (1981) have shown that cholesterol was esterified more selectively with oleic than with palmitic acid. A marked increase of cholesteryl oleate and a decrease of cholesteryl palmitate in the hepatic endoneurium of our patient (see Table) illustrates a similar preference.

Another striking lipid abnormality was the almost complete depletion of triacylglycerol in the patient's hepatic nerve, sciatic nerve, liver and skin tissues. We postulated that this deficiency of triacylglycerol might be related to the reduction in the patient's body weight (~ 7 kg in three months) before his death. However, skin samples obtained from two control patients with more severe cachexia than exhibited by our patient did not show such a dramatic loss of triacylglycerol (fig. 4). This patient had been on several drugs including insulin, prednisone, frusemide, spironolactone, diazepam and promethazine. Whether the marked reduction of tissue triacylglycerol was drug-related or represents another metabolic abnormality remains unknown. The need to study the plasma and tissue lipids before and after death in patients such as this is apparent.

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DISTURBANCES OF LONG-TERM MEMORY IN APHASIC PATIENTS

A COMPARISON OF ANTERIOR AND POSTERIOR LESIONS

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SUMMARY

The performance of 20 aphasic patients on a verbal list-learning task was examined in relation to site of lesion, as documented by CT scan. Patients with lesions of the inferior frontal lobe and/or the basal ganglia were severely impaired in both acquisition and long-term retention of the list, while the performance of patients with posterior temporoparietal involvement was nearly normal. These results contrasted sharply with scores on short-term memory tests by the same patient groups which showed an opposite trend. The findings support a functional and neuroanatomical dissociation of short and long-term memory systems and suggest that neural connections of the inferior frontal lobe and the basal ganglia may be crucial for initiating the retrieval process.

INTRODUCTION

To our knowledge, the nature of long-term memory deficits and their neuroanatomical correlates in patients with aphasia has not been investigated systematically. This is due in part to the inherent difficulty of differentiating memory disturbances from primary language disorders and the fact that aphasia-producing vascular lesions usually do not compromise the classical memory areas. Impairment of short-term memory is frequently cited in association with aphasic disorders of repetition, although it has been claimed that the defect is specific to the auditory modality (Warrington and Shallice, 1969; Warrington *et al.*, 1971; Saffran and Marin, 1975; Shallice and Warrington, 1977; Basso *et al.*, 1982). These patients are sometimes described as 'normal' in their acquisition of new verbal material and exhibit intact long-term recall, implying a functional and possibly anatomical dissociation of short- and long-term memory systems.

Our current understanding of the neuroanatomical substrate of long-term memory is based primarily on patients with lesions of the mesial temporal area and diencephalon. Surgical destruction of the left mesial temporal lobe, including the hippocampus, results in a significant reduction of some aspects of verbal memory,

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including recall of prose material and paired associate learning (Milner, 1958, 1968; Corsi, 1969), while bilateral lesions of this area lead to a global amnesia (Milner, 1972). Medial diencephalic lesions also produce an amnestic syndrome. Post-mortem examination of patients with Korsakoff's syndrome related to alcoholism reveal lesions of the dorsomedial nucleus of the thalamus and other structures surrounding the third ventricle, while the mesial temporal area is usually spared (Victor *et al.*, 1971). A relatively pure case of verbal amnesia involving traumatic lesion in the area of the dorsomedial nucleus has been studied extensively (Squire and Slater, 1978; Squire and Moore, 1979; Squire and Cohen, 1982). This patient (N.A.) exhibits the verbal learning and retention deficits of an alcoholic Korsakoff patient without the associated behavioural abnormalities or other intellectual changes.

In contrast, little is known about the role of the neocortex in verbal memory or the contribution of primary language skills to mnemonic processing. This report describes the performance of two groups of aphasic subjects with anterior and posterior lesions of the language zones on a test of verbal learning and long-term retention. We were particularly interested in the performance of patients with posterior temporoparietal lesions because of the importance of this area for auditory language processing in general and its potential significance as a cortical memory storage site. It was suggested that learning and recall would be most impaired in this group despite sparing of the mesial structures.

METHODS

Subjects

The experimental sample consisted of a consecutive series of 54 aphasic patients completing a longitudinal study of recovery from aphasia conducted at Hennepin County Medical Center between 1977 and 1983. The patients previously were neurologically normal, right-handed native speakers of English, who suffered an ischaemic infarction of the left cerebral hemisphere. There were 39 males and 15 females, ranging in age from 31 to 75 years. They were evaluated for recovery from aphasia and other neurological and neuropsychological impairments at monthly intervals for the first six months postonset. The data reported here were obtained at six months postonset in most cases, representing chronic stage performance. Lesion size and location were determined in all cases by CT scans obtained at approximately five months postonset using a Siemens Somatom II scanner. The degree of involvement of various cortical and subcortical structures was rated independently by a neuroradiologist without knowledge of the behavioural data. A four-point scale was used with (1) indicating up to 25 per cent involvement of the structure, (2) from 25 to 50 per cent, (3) from 50 to 75 per cent and (4) from 75 to 100 per cent involvement. Volume of lesion was calculated by a computer program that summed the areas of impairment traced with a cursor by the neuroradiologist in all overlapping 2 mm sections in which the lesions were present.

Two patients who did not participate in the longitudinal recovery project were included in the experimental group. Both these patients were more than six months postonset at the time of the testing. One had suffered a left intracerebral haemorrhage, the other, an ischaemic infarction.

Based on CT scan findings, the patients were divided into anterior/basal ganglia (referred to below as anterior) and posterior lesion groups for the initial analysis of both language and memory data. Subjects were placed in the anterior group if they had greater than 50 per cent involvement of the inferior frontal lobe or subcortical structures deep to this region. Areas involved included the inferior frontal gyrus and underlying white matter, the basal ganglia, anterior insula and the anterior deep white matter (corona radiata). With two exceptions, none of the subjects in this group had significant cortical convexity involvement posterior to the rolandic fissure. Two patients, A040 and A054, had small posterior lesions that did not involve the posterior temporal or supramarginal language zones. Subjects assigned to the posterior group all had some involvement of posterior language cortex including greater than 50 per cent destruction of at least one or more of the following areas: posterior insula, posterior temporal lobe, temporoparietal junction and the supramarginal gyrus. Most patients in the posterior group also had involvement of the corona radiata. These subjects did not have lesions anterior to the rolandic fissure with the exception of patient A099, who had a small superficial lesion of the precentral gyrus in addition to his posterior lesion. Since the damage did not include the inferior frontal gyrus or deep frontal stuctures (criteria for inclusion in the anterior group), he was not excluded as a posterior subject. Schematic representations of areas of lesions for patients in both groups are shown in figs. 1 and 2, and individual ratings of relevant structures are listed in Table 1. Patients with lesions that included both anterior and posterior language areas were eliminated from further analysis leaving a total of 10 subjects in the 'anterior' group and 10 in the 'posterior' group.

A normal control group included 3 male and 8 female subjects without history of central neurological abnormality (mean age 64 yrs). The control subjects were administered all memory and IQ measures described below but were not given standardized tests of language function. Demographic data for each group, as well as mean WAIS Performance IQs and test quotients on the Porteus Mazes, are presented in Table 2. The average aphasia severity rating for both patient groups based on the Boston Diagnostic Aphasia Examination are also reported.

Procedure

The degree of language impairment was determined for all aphasic subjects based on the Neurosensory Center Comprehensive Examination for Aphasia (NCCEA), (Spreen and Benton, 1969), the Boston Naming Test (Kaplan *et al.*, 1978) and the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass and Kaplan, 1972).

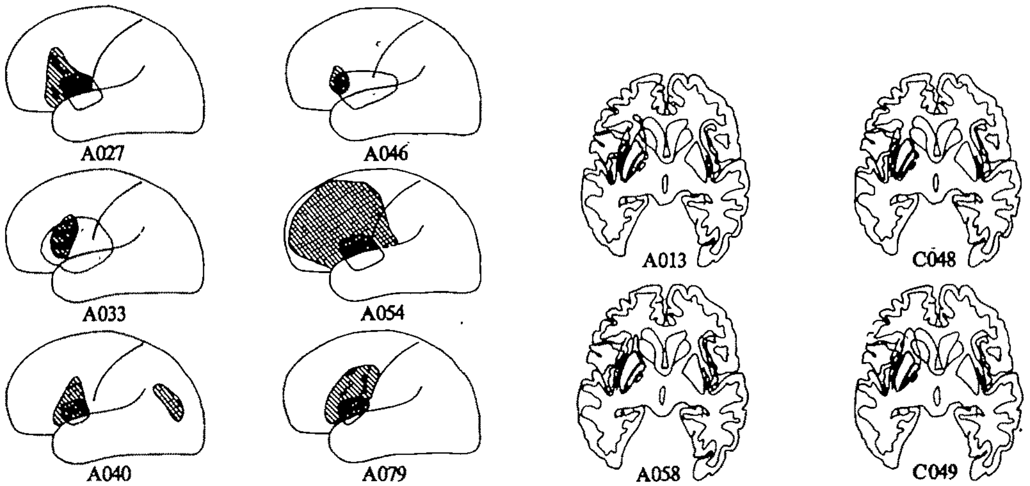

FIG. 1. Approximate areas of destruction based on CT scan ratings for patients in the 'anterior/basal ganglia' lesion group. A longitudinal view is presented for those patients whose lesions were exclusively subcortical. Cross hatching represents superficial cortical damage, while shaded areas are deep to the cortex.

TABLE 1. DEGREE OF INVOLVEMENT OF 11 SEPARATE ANATOMICAL AREAS, AND LESION VOLUME IN PATIENTS WITH ANTERIOR AND BASAL GANGLIA INVOLVEMENT (*ABOVE*) AND POSTERIOR SYLVAN INVOLVEMENT (*BELOW*)

Anterior group	*PIF*	*LRM*	*LRS*	*SM*	*A*	*PST*	*AI*	*PI*	*PGP*	*ADW*	*PDW*	*LV* (*cm*^{3})
A013	−	−	−	−	−	−	+	+	++	+	−	18.6
A027	++	+	−	−	−	−	++	+	++	−	−	34.6
A040	++	+	−	−	++	−	+	−	−	−	−	30.9
A046	−	−	−	−	−	−	++	++	−	−	−	15.5
A054	++	++	++	−	−	−	++	++	−	++	−	115.1
A058	−	−	−	−	−	−	−	−	++	+	−	9.3
A079	++	++	−	−	−	−	+	−	−	−	−	37.7
A033	+	+	−	−	−	−	++	+	++	++	+	
C048	−	−	−	−	−	−	−	−	++	−	−	
C049	−	−	−	−	−	−	−	−	++	++	+	
Posterior group												
A007	−	−	−	++	+	++	−	+	−	−	−	38.0
A011	−	−	−	+	++	−	−	+	−	−	+	31.5
A030	−	−	−	−	−	++	−	−	−	−	−	29.5
A031	−	−	−	+	−	−	−	−	−	−	+	46.6
A038	−	−	++	++	+	+	−	+	−	−	+	42.0
A087	−	−	−	++	++	++	−	−	−	−	−	36.0
A094	−	−	−	−	+	++	−	+	−	−	−	21.4
A099	−	++	−	+	−	+	−	+	−	−	−	24.3

Lesion volume was not available for 3 patients of the anterior-basal ganglia group. PIF = posterior frontal; LRM = lower rolandic, motor; LRS = lower rolandic, sensory; SM = supramarginal gyrus; A = angular; PST = posterior superior temporal; AI = anterior insula; PI = posterior insula; PGP = putaman-globus pallidus; ADW = anterior deep white matter; PDW = posterior deep white matter; LV = lesion volume in cm^3. − = no or minimal involvement; + = definite involvement up to approximately 50 per cent; + + = severe involvement.

Verbal learning and retention were evaluated using a 9 word list learning task which employed the selective reminding technique on successive learning trials (Buschke, 1973). The items were high frequency nouns chosen from 3 semantic categories. The 3 items within each semantic category began with different phonemes, but the same 3 phonemes were represented in each of the 3 semantic categories. The list was read aloud by the experimenter at the rate of one item every 2 s. The first recall attempt followed immediately and the subject was asked to name as many items as he could in any order (although the order of recall was recorded). When the patient had produced all the items he could remember, he was then reminded only of the items he had failed to name. This was followed by a second attempt at recall of the entire list and selective reminding of items missed. Learning trials were repeated in this way until the patient named all 9 words on a single trial, or until 10 learning trials had been completed. Using the criteria suggested by Buschke, an item was judged to be stored in long-term memory after it had been recalled spontaneously on 2 successive trials, and any subsequent recall of that item was called a long-term retrieval. Items that were recalled only following a reminder were said to be examples of short-term retrieval. Long-term retention of the list was assessed in a single recall trial without reminding following a 60 min delay. During the delay period, subjects were engaged in a battery of nonverbal cognitive tests. Immediately after the long-term recall attempt, all subjects were presented with a brief recognition test of the same target items. The recognition test consisted of 20 high frequency nouns, including the 9 items in the original list and 11 filler items unrelated to the target stimuli. The list was read to the subject at the rate of one item every 2 s, and the subject was asked to raise his hand when he heard a word from the original list.

For all aphasic subjects, immediate memory was also evaluated with a series of digit span tests presented in both the auditory and visual modalities. In the auditory condition, digits were read aloud by the examiner. In the visual conditions, numbers were serially projected on a screen directly in front

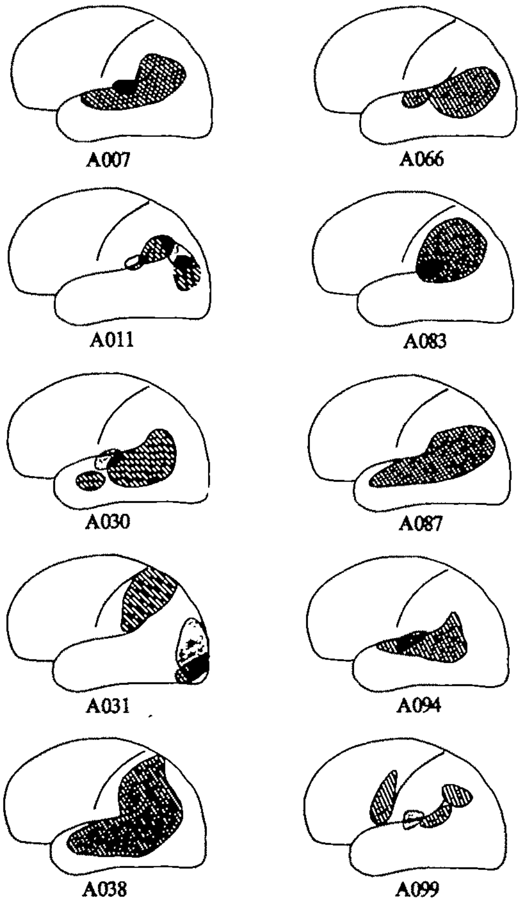

FIG. 2. Approximate areas of destruction based on CT scan ratings for patients in the 'posterior' lesion group.

TABLE 2. DEMOGRAPHIC INFORMATION, MEAN TEST SCORES AND LESION VOLUME RATINGS FOR ANTERIOR AND POSTERIOR LESION GROUPS AND NORMAL CONTROL SUBJECTS

Groups	*n*	*Age*	*Sex*		*Mean WAIS performance IQ*	*BDAE severity*	*Porteus Mazes Test quotient*	*Lesion volume (cm^3)*
			M	*F*				
Anterior	10	59.7 (8.4)	6	4	111 (12.3)	3.4 (1.1)	100 (17.0)	37 (35.8)
Posterior	10	61.9 (7.6)	9	1	106 (12.6)	3.4 (0.5)	90 (29.5)	36.7 (14.1)
Normals	11	63.8 (9.2)	3	8	110 (10.2)			

Figures in brackets indicate standard deviations.

of the subject. Immediately following the stimulus presentation, the subject was requested to point in sequence to the correct digits on a card containing a 3 × 3 sequential array of the digits 1 to 9. In each condition, the maximum span for a given subject was established using the standard procedure of Wechsler (1945) with a presentation rate of one item/s. All trials were then repeated with the interval between digits increased to 3 s. However, since no systematic differences were noted based on presentation rate, the data reported here are mean scores for the 'fast' and 'slow' conditions combined.

Finally, all subjects were administered the Performance subtests of the *Wechsler Adult Intelligence Scale* and the *Porteus Mazes*..

RESULTS

The two lesion groups did not differ in overall severity of aphasia as determined by BDAE ratings (Table 2), and performed similarly on a number of language measures (fig. 3). With one exception (A054), all patients in both groups were classified as fluent (BDAE) at the time of memory testing, although some patients in the anterior group had been nonfluent in the acute stage. Anterior patients, as a group, were slightly superior to the posterior lesion group in auditory comprehension as measured by the NCCEA version of the Token Test ($P < 0.02$), and also scored slightly higher on 'Verbal Expression'. This measure represents the combined mean score of the 'Sentence Construction' and 'Description of Use' subtests from the NCCEA. In contrast, the average scores of posterior lesion patients were above those of the anterior group on the *Boston Naming Test* and two measures of word fluency. These included the NCCEA 60 s oral fluency for each of the letters F, A and S, and the 60 s Animal Fluency subtest from the BDAE. However, these group differences were not statistically significant based on t-tests.

Results of the verbal list-learning task revealed marked differences between groups. The averaged acquisition scores for both patient groups and the normal control subjects over 10 learning trials are presented in fig. 4. The two lesion groups started at the same level, recalling around 3 items on the first trial. Contrary to expectation, the posterior group improved rapidly, attaining an average recall score of about 7 items by the tenth trial. Although the absolute level of performance was

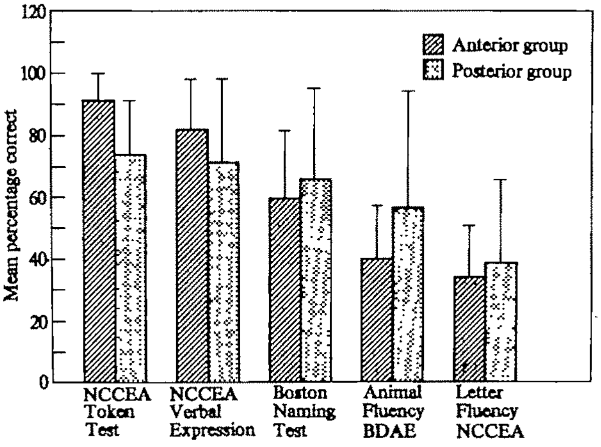

FIG. 3. Performance of two lesion groups on language measures. NCCEA = Neurosensory Center Comprehensive Examination for Aphasia; BDAE = Boston Diagnostic Aphasia Examination. Vertical bars indicate standard deviations.

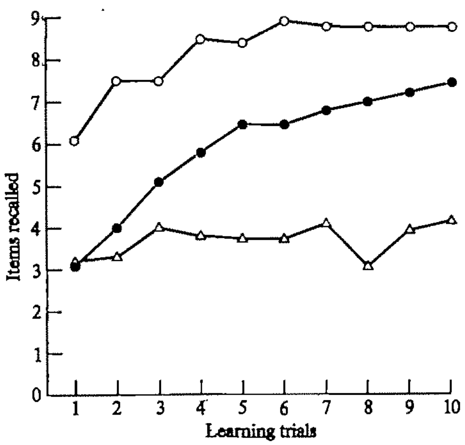

FIG. 4. Mean number of items recalled on each of 10 successive learning trials by anterior (△—△) and posterior (●—●) lesion groups and normal control subjects (○—○) with selective reminding of items missed followed each recall attempt.

reduced in comparison to control subjects, the pattern of learning in the posterior group appeared qualitatively normal. Patients with frontal or basal ganglia lesions, however, made little progress, recalling an average of only 4 items after 10 learning trials. A one-way analysis of variance with repeated measures performed on the acquisition scores across trials indicated a significant group effect F (2, 18) = 28.4, $P < 0.001$, and a group by trials interaction F (18, 252) = 4.1, $P < 0.001$. Examination of group contrasts revealed a significant difference between each patient group and normal controls on the first trial (anteriors *vs* controls $P < 0.001$; posteriors *vs* controls $P < 0.001$), while there was no difference between normals and posterior lesion subjects ($P = 0.165$) by the tenth trial. The recall performance of the two lesion groups was significantly different on the tenth trial ($P < 0.002$).

The number of short- and long-term retrievals across trials is presented in fig. 5 for all three groups. Seventy-nine per cent of the responses produced by the anterior

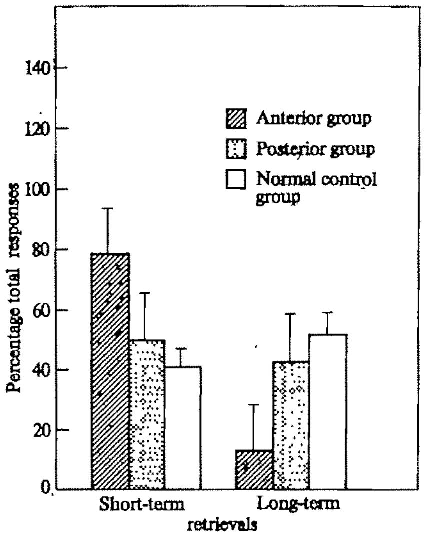

FIG. 5. Percentage of total responses classified as short- or long-term retrievals according to criteria described in the text. Vertical bars indicate standard deviations.

lesion patients were examples of short-term retrieval by the criteria described above, while only 13 per cent were long-term retrievals. For the posterior patients and normal control subjects, group averages for the two response types were nearly equivalent.

Fig. 6 illustrates the 60 min recall and recognition scores for each group. The anterior group was severely impaired in long-term recall (26 per cent correct) while the posterior and control groups recalled 73 and 81 per cent of the list, respectively, without cueing. A one-way analysis of variance yielded a significant group effect F (2, 26) = 11.3, $P < 0.001$, with group contrasts indicating that the anterior subjects had significantly poorer recall than both the posterior patients ($P < 0.001$) and the normal controls ($P < 0.001$). The difference in recall scores between the posterior lesion group and control subjects was not statistically significant ($P = 0.40$). On the recognition task, however, the performance of the anterior group improved considerably to 79 per cent correct resulting in an insignificant group effect F (2, 26) = 1.6, $P = 0.212$.

Results of the digit span tests are illustrated in fig. 7. In contrast to the learning task, patients with anterior lesions attained higher span scores than posterior lesion subjects. A one-way analysis of variance comparing mean auditory digit span scores for all three groups was highly significant F (2, 25) = 15.75, $P < 0.001$. The posterior lesion group performed significantly worse than the normal controls ($P < 0.001$) and the anterior lesion subjects ($P < 0.001$), while the difference between the anterior group and normal controls was not significant ($P = 0.114$). The anterior group was also superior to posterior lesion subjects on the visual digits test ($P < 0.05$).

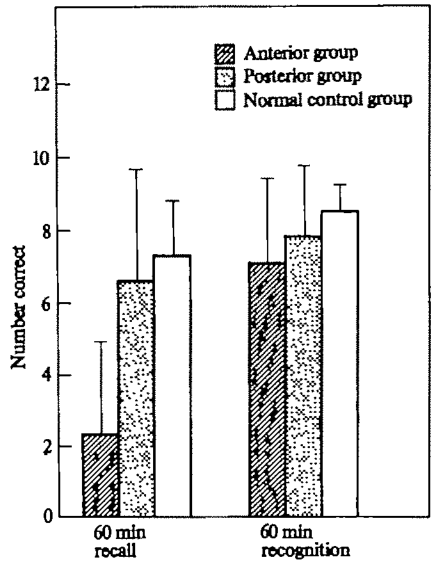

FIG. 6. Mean 60 min recall and recognition scores on the list-learning task by anterior and posterior lesion patients and normal subjects. The maximum number correct is 9. Vertical bars indicate standard deviations.

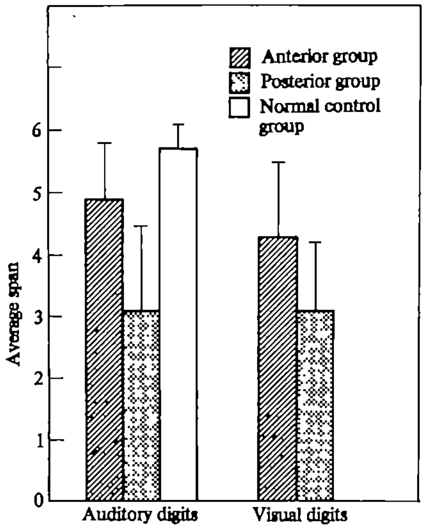

FIG. 7. Average digit span scores for auditory and visual presentations by anterior and posterior lesion patients and normal control subjects. The maximum span tested was 6. Vertical bars indicate standard deviations.

DISCUSSION

These results suggest that portions of the left inferior frontal lobe and the basal ganglia may play an important role in establishing and/or retrieving new verbal memories. This finding is in marked contrast to the predicted outcome that long-term verbal memory would be more severely affected by destruction of the posterior temporoparietal area in patients with aphasia. The possibility that the impairment of the anterior group might be secondary to a particular aspect of the language disorder, such as impaired auditory comprehension or spontaneous verbal expression, is unlikely given the similar performance of the two lesion groups on most language tasks. Although some patients in the anterior group were nonfluent in the acute period, all but one (Case A054) were classified as fluent by the BDAE at the time of testing six months postonset and none demonstrated the paucity of spontaneous speech characteristic of patients having transcortical motor aphasia. The anterior group was, in fact, slightly superior to the posterior group on the verbal expression subtests of the NCCEA.

The possibility that poor acquisition scores may have reflected a tendency to perseverate preceding responses by patients in the anterior group is not supported by the data. In the selective reminding paradigm the subject is reminded only of the items that he failed to recall on the previous trial. Patients with anterior lesions tended to repeat the items they had just heard, rather than perseverating their previous responses. Behaviourally, the patients with anterior lesions did not present frontal lobe symptoms. They were socially appropriate with little evidence of psychomotor retardation and appeared to exercise good judgement including methodical approaches to problem solving. Their scores were superior to those of the posterior group on the Porteus Mazes (Table 2).

It appears, then, that failure on the verbal list learning task by aphasic patients with anterior lesions reflects a relatively pure deficit of learning and/or long-term retrieval. It is proposed that this memory impairment is a direct result of insult to a critical region connecting frontal language cortex to subcortical components of the hippocampal-diencephalic memory complex. This hypothesis is supported by a number of anatomical studies in man and other primates, demonstrating well-established pathways between frontal cortex and mesial temporal areas (Van Hoesen *et al.*, 1975), as well as reciprocal connections between the thalamus and frontal lobes (Walker, 1966). The finding of good recognition performance in the anterior group supports the possibility that retrieval processes may be more disrupted than encoding functions. If this is the case, we must assume that some learning has occurred, but that access to the information is somehow impeded during retrieval attempts. This impediment could be described as a failure to initiate an effective search of long-term memory, a role that might be ascribed to the left frontal lobe. Although not statistically significant, the relative naming and verbal fluency deficits in the anterior group (noted above) may be another manifestation of retrieval failure. This cannot be said of the posterior group whose confrontation naming did not differ significantly from the anterior patients, but whose long-term word retrieval was nearly normal.

The remarkable success of the posterior group on the list-learning task is of considerable interest. Despite average pointing digit spans of only 3 items, the majority of these subjects succeeded in learning a 9 word list with selective reminding and recalled it well after a one-hour delay. A possible strategy responsible for this success is suggested by the relatively higher incidence of categorized responses compared to anterior cases. Twenty-seven per cent of all responses were contiguous with an item from the same category for the posterior group (30 per cent for normals), while only 16 per cent of responses by the anterior patients fit this criterion. Perhaps the posterior patients were able to learn by relying on semantic association since skills necessary for rote rehearsal were severely impaired. Semantic learning is known to be more durable than rote learning and might have contributed to the successful recall by patients in this group. Anterior patients, on the other hand, may be deficient in associative thinking and unable to compensate this loss despite well-preserved repetition skills. The data suggest, therefore, that the naming deficits in the two groups reflect interference with different stages of word retrieval.

The success of the posterior group argues against a significant role for the posterior language cortex in verbal memory storage since 7 of the 10 subjects had greater than 50 per cent destruction of either the posterior superior temporal area or the supramarginal gyrus. This finding supports the contention of Warrington and Shallice (1969), and others (Warrington *et al.*, 1971; Basso *et al.*, 1982) that short- and long-term memory systems are both functionally and anatomically dissociated.

The suggestion that the frontal lobes may be involved in memory processing is not new. Learning deficits have been reported on delayed matching and delayed alternation tasks following removal of frontal cortex in monkeys (Mishkin, 1957; Gross and Weiskrantz, 1964; Mishkin *et al.*, 1969; Stamm, 1970; Stamm and Weber-Levine, 1971) and similar impairment has resulted from lesions or electrical stimulation involving the head of the caudate nucleus and the posterior sulcus principalis (Mishkin and Pribram, 1955; Dean and Davis, 1959; Battig *et al.*, 1960; Stamm, 1961; Mishkin *et al.*, 1969). In man, deficits in maze learning and other complex problem-solving tasks have been associated with frontal lobe excisions (Milner, 1964). However, since the behaviour of these patients is frequently described as impulsive or perseverative, the relative contribution of a memory factor is difficult to quantify.

Recently, Petrides and Milner (1982) found marked deficits on a series of simple self-ordered tasks by patients with surgical excisions of dorsolateral frontal cortex, particularly in the left hemisphere. They suggested that the impairment may be a type of short-term memory deficit related to poor organizational strategies, or the inability to monitor responses. Direct comparison of these surgical cases with our anterior patients is not appropriate, however, since the groups differed markedly in the size as well as location of the damaged area.

The unique contribution of the frontal language cortex and related subcortical structures to long-term memory processing cannot be determined in detail by our limited data. We have demonstrated, however, that performance on a verbal learning task may be selectively disrupted by damage to areas of the brain previously not considered critical to human memory function. The ultimate significance of this unexpected association must be clarified through further research.

ACKNOWLEDGEMENTS

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EXPERIMENTAL GAZE PALSIES IN MONKEYS AND THEIR RELATION TO HUMAN PATHOLOGY

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SUMMARY

Lesions were placed in the paramedian pontine reticular formation (PPRF) of monkeys and the resulting gaze palsies studied. Brainstem regions were identified by single cell recordings before kainic acid was injected to selectively destroy neuronal cell bodies in the vicinity.

Unilateral PPRF lesions led to a loss of all rapid eye movements towards the ipsilateral side. Deficits were identical to those after experimental electrolytic lesions in monkeys, or structural lesions in humans.

Bilateral PPRF lesions produced two different syndromes. Rostral PPRF lesions led to a selective loss of horizontal rapid eye movements leaving vertical movements intact. Caudal PPRF lesions led in addition to a severe disruption of vertical rapid eye movements.

INTRODUCTION

Several different types of eye movements can be distinguished: rapid (saccades and quick phases of nystagmus), slow (pursuit and slow phases of nystagmus), and vergence. Such a classification has proved useful because premotor pathways for these functions are partially separate and can therefore be affected to a different degree in pathological conditions. Because the two eyes generally move in tandem, a central generator for eye movements can treat them as a single organ, the 'double eye' of Hering (1868; literal translation of *Doppelauge*). This concept requires that descending cortical pathways do not directly synapse on motoneurons, but instead on intermediate cells in the brainstem (*Schaltzellen*, von Monakow, 1905) which in turn distribute the strength of innervation to the three pairs of muscles for each eye. On clinical grounds, these intermediate cells, constituting a 'gaze centre', had been localized in the pons for horizontal gaze and in the pretectum of the mesencephalon for vertical gaze. A number of brainstem syndromes featuring gaze palsies were described in the last century (Foville, 1858; Wernicke, 1877; Parinaud, 1883). Much remained as speculation until Bender and his associates began exploring the

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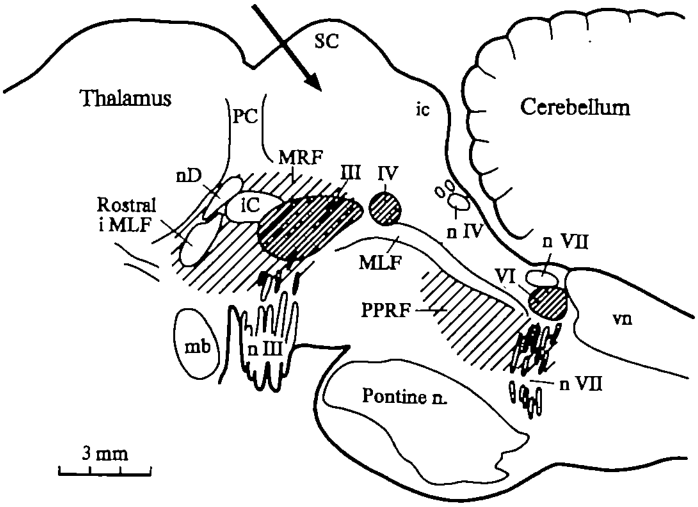

FIG. 1. Parasagittal cut through the brainstem of a rhesus monkey. The third, fourth and sixth nuclei are heavily shaded. The paramedian pontine reticular formation (PPRF) and the rostral interstitial nucleus of the MLF (rostral iMLF) are immediate premotor areas for generation of horizontal and vertical rapid eye movements. iC = interstitial nucleus of Cajal; mb = mammillary body; nD = nucleus of Darkschewitsch; PC = posterior commissure; MRF = mesencephalic reticular formation; MLF = medial longitudinal fasciculus; sc and ic = superior and inferior collieuli; vn = vestibular nuclei (from Henn *et al.*, 1982*a*). Arrow indicates vertical stereotaxic plane.

oculomotor system in the rhesus monkey with stimulation and lesion studies in a systematic way (Bender and Shanzer, 1964).

A synthesis of present knowledge based on neurophysiological and anatomical research is represented by diagrams in the first two figures. Fig. 1 outlines the relevant anatomical structures for gaze control: the paramedian pontine reticular formation (PPRF) for generating eye movements in the horizontal plane, and the rostral interstitial nucleus of the medial longitudinal fasciculus (rostral iMLF) for generating eye movements in the vertical plane. A functional interrelationship between these areas is proposed schematically in fig. 2. These areas are part of the brainstem reticular formation.

The concept of the reticular formation has undergone several changes since Moruzzi and Magoun (1949) defined it functionally. They obtained a general activating response with electrical stimulation from an area overlapping but not identical to a region defined anatomically by large neurons with a wide distribution of dendrites and usually many axon collaterals. Brodal (1957) described several subregions within the reticular formation. The concept that parts of it control specific motor function was corroborated by the systematic lesion studies of Bender and Shanzer (1964) who produced gaze palsies experimentally in monkeys. The relevant area in the pontine reticular formation was further elaborated by Cohen *et al.* (1968), who introduced the term PPRF. This region was defined functionally as the area which after a lesion leads to a gaze palsy to the ipsilateral side (Goebel *et al.*, 1971). It comprises medial portions of the nucleus reticularis magnocellularis (or nucleus centralis pontis oralis and caudalis). In the monkey there are two major efferent pathways from the PPRF. The first is to the rostral interstitial nucleus of the medial longitudinal fasciculus to coordinate horizontal and vertical movements. The second is to the ipsilateral abducens nucleus and from there, *via* internuclear neurons, to medial rectus motoneurons of the contralateral side to direct horizontal gaze to the ipsilateral side (Büttner-Ennever and Henn, 1976). In addition, descending pathways to the medulla oblongata have been observed (Büttner-Ennever, 1977, 1979). Essentially the same anatomical connections have been found in the cat (Graybiel, 1977*a*, *b*). Functional subdivisions of the PPRF as suggested by physiology have not yet been determined anatomically. Single neuron studies in this area in the monkey showed a diversity of eye movement-related neurons (Cohen and Henn, 1972*a*, *b*; Luschei and Fuchs, 1972; Keller, 1974).

The generation of rapid eye movements consists of several parallel processes. In separate channels the geometric parameters of horizontal or vertical movement components are elaborated, and in a further channel timing and coordination of movement components are effected (Robinson, 1975; Keller, 1980, 1981; Hepp and Henn, 1983). For horizontal movements the earliest information can be found in the rostral PPRF. Neurons there are mostly of the long-lead burst type, that is, they are activated more than 12 ms before the onset of a saccade and they fire maximally for movements of a specific amplitude and direction. This information is transmitted to the caudal PPRF. Neuronal activity there has latencies shorter than 12 ms on average, and neurons increase their firing rate with an eye displacement in the pulling directions of the eye muscles. In the medial PPRF a high percentage of neurons are pause cells: they fire continuously with a frequency of 150 to 200 Hz during fixation periods or slow eye movements, and are totally inhibited

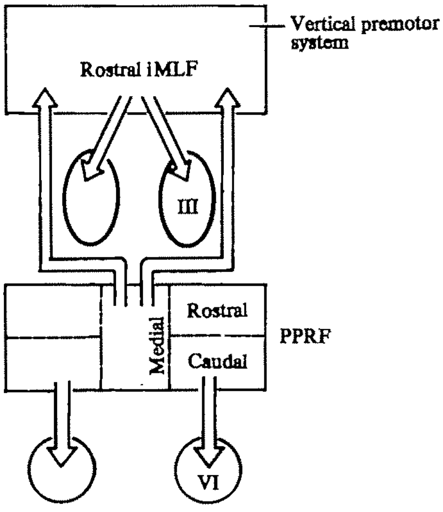

FIG. 2. Scheme of rapid eye movement generation. The medial PPRF triggers and synchronizes eye movements in the horizontal and vertical directions. Vector parameters of horizontal eye movements are elaborated in several steps in the rostral and caudal PPRF; determination of vertical movement parameters is achieved in the rostral iMLF. III = oculomotor complex; VI = abducens nucleus.

immediately before and during rapid movement. These neurons, together with their mirror image neurons which exhibit a short burst with movements in all directions, could coordinate the onset and the combination of horizontal and vertical movement components. Neurons in the rostral iMLF have not been explored in such great detail. They seem to contribute the vertical counterpart to the neurons in the caudal PPRF for horizontal movements.

Based on this scheme different deficits would be expected when lesions are placed in subdivisions of the PPRF. Some preliminary results have been reported (Henn *et al.*, 1982*a*, *b*; Lang *et al.*, 1982).

METHODS

Experiments were performed on 5 juvenile Rhesus monkeys (*Macaca mulatta*) and 1 *Cercopithecus aethiops*. Under halothane-nitrous oxide inhalation anaesthesia, initiated by pentobarbitone, the following items were permanently implanted: (1) a receptacle which later held the microdrive with the microelectrode placed stereotactically over a trephine hole; (2) silver-silver chloride electrodes around the bony orbit for monitoring eye position; and (3) bolts attached to the skull to fix the head during experiments. The experiments were started about a week after this operation. One animal was trained to fixate a stationary or moving light according to the paradigm of Wurtz (1969). In the other untrained animals eye movements were calibrated by animal rotation at a constant velocity of 30 deg/s about their vertical and horizontal axes. Optokinetic nystagmus (OKN) then has a gain of unity (Cohen *et al.*, 1977). Usually, 1 mV of induced electro-oculogram (EOG) voltage corresponds to 12 deg position change in the horizontal, or 15 deg in the vertical direction. Such measurements were taken repeatedly before the lesion for each animal and used as calibration for postlesion measurements. In all animals, single unit recordings were obtained prior to the lesions and will be reported elsewhere.

Chemical lesions were produced with kainic acid (Coyle *et al.*, 1978; McGeer *et al.*, 1978). It was concentrated to 4 to 8 μg/μl, was dissolved in 0.2 M phosphate buffer, and had a pH of 7.4. The total amount of injected kainic acid was between 0.8 and 1.6 μl. The region was identified by single unit recordings with tungsten electrodes advanced through a guide tube with an outer diameter of 0.9 mm. Then the electrode was withdrawn with the guide tube left in place. Subsequently the glass micropipette was advanced through the guide tube with the tip protruding the same length as the tungsten recording electrode. Immediately before the injection dexamethasone was given (4 mg i.m.). The entire volume of kainic acid was delivered in several steps over a period of 20 to 30 min. With a successful injection deficits appeared within 30 min, usually quickly increasing to a total ophthalmoplegia. Animals then received 5 mg diazepam i.m., in an attempt to prevent generalized seizures. Within 24 h symptoms gradually regressed to a state in which deficits were unchanged over the observation period of several weeks. Animals were tested clinically on a daily basis. More extensive testing with quantitative monitoring of eye movement during vestibular and optokinetic stimulation was undertaken at least every week. Film records were made of the eye movements during spontaneous movements and during animal rotation in the light. In some animals single neuron recordings were performed in other undamaged oculomotor areas of the brainstem. After a survival time between one and six weeks, the animals were killed. Under deep pentobarbitone anaesthesia they were perfused with 200 ml of 6 per cent plasma expander (dextran) containing 2 ml of heparin (10 000 units). This was followed by 4 per cent paraformaldehyde in phosphate buffer at pH 7.4. Afterwards the brain was kept in fixative for about 16 h and finally transferred to a 0.1 M phosphate buffer, 30 per cent sucrose, solution for two to three days. Frozen sections of 30 μm thickness were cut in the coronal plane, extending from the nucleus prepositus hypoglossi to the posterior commissure. Every third section was stained with cresyl violet and luxol fast blue for cell bodies and myelin. One animal was processed for electron microscopy with special perfusion and fixation techniques.

RESULTS

Neuropathology of Kainic Acid Lesions

The morphology of kainic acid lesions showed time-dependent changes. Within a survival time of one week, severe neuronal cell loss, infiltration of perivascular mononuclear cells and some microglial cells were observed. After a survival time of three to four weeks the lesions contained predominantly macrophages and were relatively well demarcated from the neighbouring brain tissue (fig. 3). With a survival time of six weeks, proliferation of astrocytes was predominant. In all cases there was virtually a complete loss of neuronal cell bodies within the lesions. Luxol fast blue staining revealed some preservation of myelinated fibres. Specifically, abducens nerve rootlets traversing one lesion stained positively with luxol fast blue. Electron microscopic examination of one case showed some myelin breakdown within the lesion, but many myelin sheaths remained unaffected.

Unilateral PPRF Lesions

Three animals were studied in this group. Neurological deficits were the same in the two animals with caudal lesions and were also the same as described earlier for electrolytic lesions. The clinical findings were that all rapid eye movements towards the ipsilateral side were lost. The eyes were mainly held in a paramedian position on the opposite side, and were not spontaneously brought into the ipsilateral hemifield.

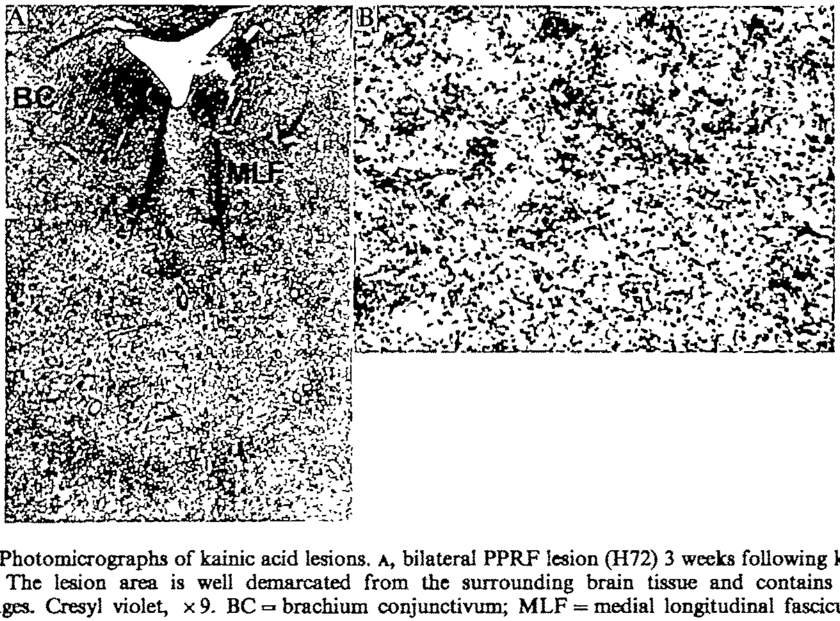

FIG. 3. Photomicrographs of kainic acid lesions. A, bilateral PPRF lesion (H72) 3 weeks following kainic acid injection. The lesion area is well demarcated from the surrounding brain tissue and contains abundant macrophages. Cresyl violet, ×9. BC = brachium conjunctivum; MLF = medial longitudinal fasciculus; ★ = artefact (wrinkle). B, histological changes in PPRF (H68) 1 week following injection of kainic acid (4 $\mu g/\mu l$). Note the absence of neuronal cell bodies, gliosis and the presence of perivascular mononuclear cell infiltration. Cresyl-violet, ×17.

In total darkness there is spontaneous nystagmus towards the contralateral side. Only during strong vestibular stimulation did the eyes cross the midline into the ipsilateral hemifield, resulting in nystagmus to the contralateral side. It is remarkable that quick phases, starting in the 'paretic' field, appeared normal, as did the slow phases when the eyes moved widely across midline. Vertical eye movements seemed to be intact. This type of lesion, especially its deficits in relation to vestibular stimulation, has recently been described (Jaeger *et al.*, 1981). One important result was that dominant time constants of compensatory movements after vestibular stimulation remained symmetrical and in the normal range (10–40 s).

One animal with a unilateral rostral lesion was studied (H69). In a second operation, the lesion was later extended bilaterally so that the effect of a right-sided unilateral lesion could be observed for one week. The syndrome essentially exhibited all the features of a one-sided caudal PPRF lesion, except that in this animal fixation was intact and there was no spontaneous nystagmus in the light and even during some periods in the dark. This animal had previously been trained for pursuit eye movements. Tracking was normal in the contralateral hemifield, but was virtually impossible in the ipsilateral field. Any saccade, instead of correcting the pursuit path, usually shifted the eyes into the contralateral hemifield.

Bilateral Caudal Lesions

The lesion locations are shown in fig. 4. In one animal (H72), the lesion extended bilaterally from the level of the nucleus prepositus hypoglossi almost to the level of the trochlear nuclei. On the left, small ventral portions of the medial vestibular

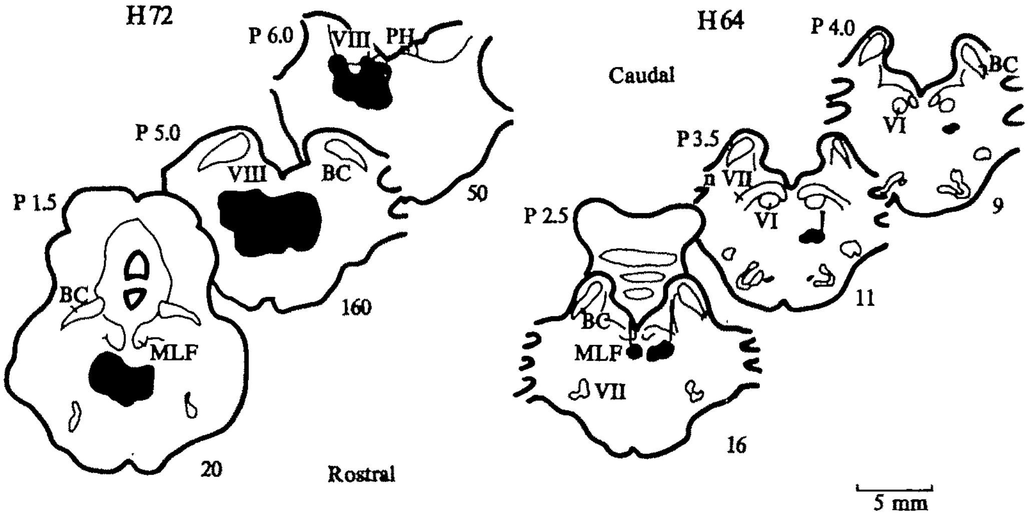

FIG. 4. Bilateral kainic acid lesions in the caudal PPRF of 2 monkeys (H72 and H64) in coronal sections. BC = brachium conjunctivum; MLF = medial longitudinal fasciculus; PH = nucleus prepositus hypoglossi; VI = abducens nucleus; VII = facial nucleus; n VII = facial nerve. Numbers above drawings of sections indicate stereotaxic coronal planes.

nucleus were affected. The lesion in the second monkey (H64) was considerably smaller, involving mainly caudal parts of PPRF ventral to the abducens nucleus.

The most striking finding was the severe disruption of rapid eye movements in *all* directions. The normal pattern of fixation with interspersed rapid eye movements was lost. In the animal with the large lesion (H72), this disruption was virtually complete, while in the animal with the much smaller lesion (H64) some rapid eye movements of small amplitude and reduced velocity to the right could sometimes be seen. Usually the animals stared straight ahead. At times, in the vertical direction, the eyes moved at varying velocities without clear fixation periods and without a clear demarcation of rapid eye movements. Although velocities at times could reach those of saccades, the velocities were unpredictable for a given amplitude. The generation of rapid eye movements, either to change direction of fixation or as quick phases of nystagmus, was lost. Blinks were normal. Vestibulo-ocular reflexes (VOR) were normal both to rotations with a sinusoidal velocity profile or with step displacements. Notably, for sinusoidal stimulations, phase angles had not changed, and after velocity steps the eye could be held in the newly acquired eccentric position. These facts show that the velocity-to-position integrator was still functional. Thresholds for vestibular stimulation were raised. Exact measurements were not attempted, since slow drifting movements intervened.

Figs. 5 and 6 show some details of eye movement deficits of animal H72. In the light as well as in the dark the animal exhibited a staring straight-ahead look with little change in horizontal eye position, but at times irregular motions in the vertical plane. Film records as well as EOG recordings show that these vertical movements were executed with randomly varying velocities. The animal was unable to hold the eyes steady and to fixate. During rotation about a vertical axis to elicit the horizontal

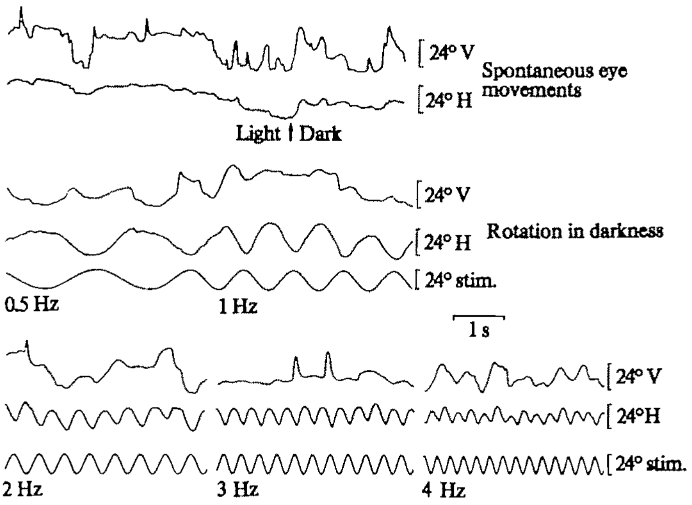

FIG. 5. Eye position recording from monkey H72 with a large bilateral mediocaudal lesion (*left side* of fig. 4). There are no rapid eye movements in the horizontal plane (H), although compensatory movements are normal and can reach high velocities. In the vertical plane (V), there are sometimes irregular high velocity oscillatory movements without intervening fixation periods.

VOR, these irregular vertical movements were mixed with the horizontal compensatory movements. The horizontal VOR was basically intact. Eye movements were always in the compensatory direction and phase angle was small (zero phase angle defined as perfect compensation). At stimulus frequencies between 0.5 and 6 Hz the phase angle was, on average, not significantly different from zero, as in the normal animal (Böhmer and Henn, 1983). Even allowing for some error in calibration, the VOR gain was near unity over a wide range of stimulus frequencies. This is shown in fig. 5 for stimulus frequencies between 1 and 3 Hz with some attenuation for a frequency of 0.5 Hz and 4 Hz. Results for the vertical VOR (fig. 6) were similar, with phase angles around zero for stimulus frequencies between 0.5 and 6 Hz. In the low frequency range, there was an increasing phase angle which did not change after the lesion.

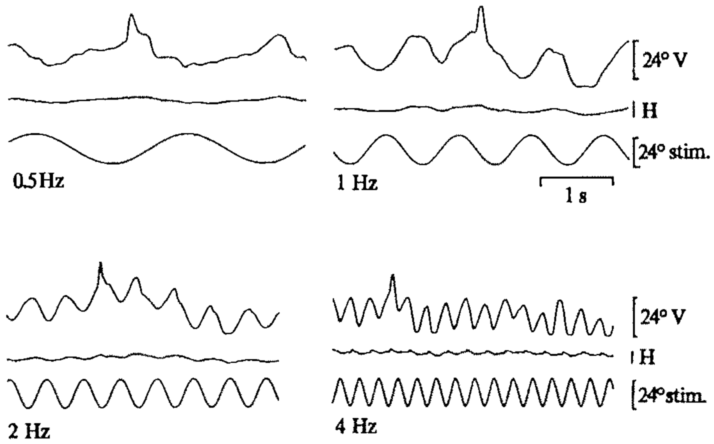

FIG. 6. Eye position recording from monkey H72 with a large bilateral mediocaudal PPRF lesion. During head pitching in the dark there are normal compensatory vertical movements.

If, during horizontal VOR testing, the stimulus amplitude was increased, the eyes remained in extreme lateral positions because there was no fast repositioning of the eyes until the stimulus movement direction was reversed (fig. 7). Gain measurements thus cannot be made at low frequencies. With low stimulus accelerations or velocities eye movements were irregular (e.g. 0.5 Hz in fig. 6). The threshold to elicit the VOR reliably was increased in all animals with caudal PPRF lesions.

During optokinetic stimulation the eyes deviated in the expected direction. If during sinusoidal stimulation the amplitude exceeded the range of normal movements, or during constant velocity stimulation, the eyes deviated towards a lateral position, and moved slowly towards midposition after the stimulus ceased.

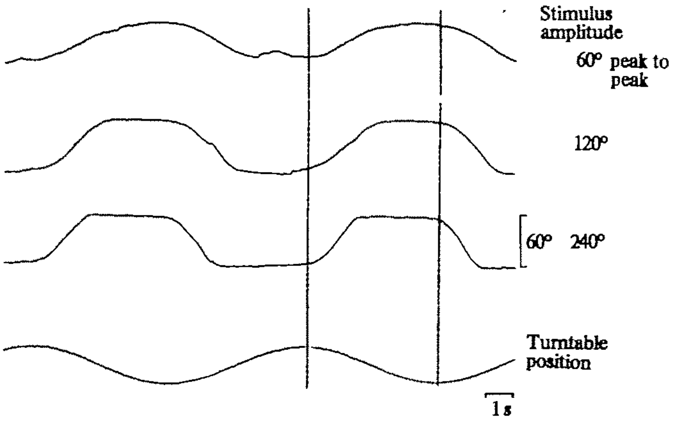

FIG. 7. Horizontal VOR in monkey H64 with a small bilateral caudal PPRF lesion. With increasing stimulus amplitudes during rotation at 0.1 Hz the eyes swing from one extreme lateral position to the other, covering an amplitude of about 60 deg, which is the oculomotor range for lateral movements in the monkey.

Animal H64 had a much smaller lesion. Some abortive rapid eye movements were possible vertically and towards the right. These movements were slowed, but could still be identified as rapid movements when occurring repetitively as in nystagmus.

Bilateral Rostral Lesions

The extent of lesions is shown in fig. 8. In both cases, the lesions reached the level of the trochlear nuclei rostrally and extended about 2 to 3 mm caudally, not reaching the level of the abducens nuclei.

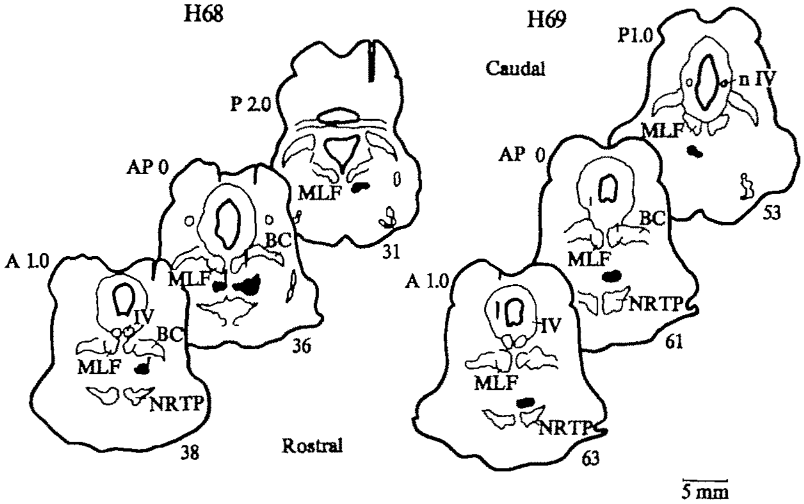

FIG. 8. Bilateral kainic acid lesions in the rostral PPRF of 2 monkeys (H68 and H69). BC = brachium conjunctivum; MLF = medial longitudinal fasciculus; n IV = trochlear nerve; NRTP = nucleus reticularis tegmenti pontis.

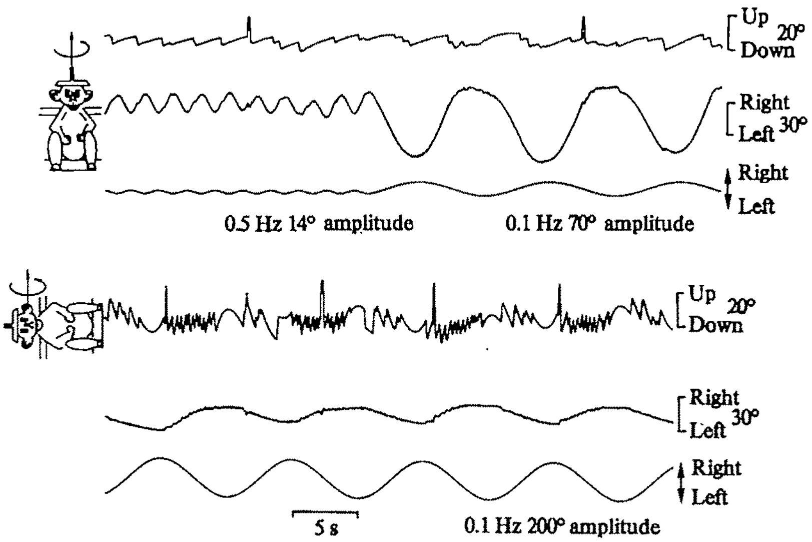

FIG. 9. VOR in the horizontal and vertical plane in animal H68. From above, vertical and horizontal eye position, and turntable position. During horizontal angular acceleration there are compensatory movements without any rapid phases, while there is little downward spontaneous nystagmus. During stimulation in the sagittal plane in normal monkeys, nystagmus occurs with higher gain in the downward direction.

The outstanding feature was loss of all rapid eye movements in the horizontal plane while vertical movements were little affected (fig. 9). More specifically, in the vertical plane, velocities of rapid movements were slightly reduced; the VOR had normal gain and phase relationships, and optokinetic nystagmus was also normal.

During horizontal VOR testing with small amplitudes, the eyes deviated with a compensatory movement in the expected direction. If the stimulus amplitude exceeded the oculomotor range, the eyes deviated into an extreme lateral position and stayed there (*see also* fig. 7). Phase angles were in the normal range between 0.005 and 5 Hz (fig. 10). Notably in the frequency range between 0.2 and 5 Hz, phase angles were around zero, indicating normal compensation. This proves that the velocity-to-position integrator had remained intact. During steps of angular displacement, the eyes deviated in the expected direction and then stayed eccentrically. In the dark they drifted back towards the primary position with a time constant greater than 10 s. With a rapid succession of up and down eye movements, often combined with blinks, the animal was able to bring the eyes back towards primary position slightly faster.

Animal H69 had a very small lesion and had preserved some ability to generate rapid movements towards the right. Yet these movements were small in amplitude and did not exceed 3 deg. During large vertical eye displacements, however, or during blinks, the eyes could be moved to about 5 deg in the horizontal direction.

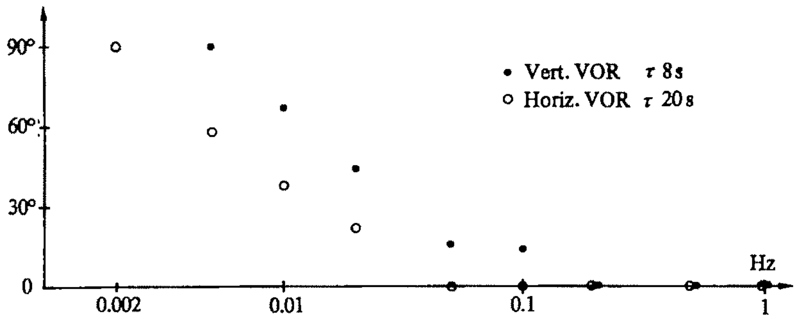

FIG. 10. Phase angles of the VOR in animal H69. Measurements of turnaround eye position *vs* peak turntable position were taken over several cycles in each direction and then averaged. At frequencies below 0.1 Hz horizontal rotation, the eyes remained in an extreme lateral position during most of the cycle before moving into the opposite lateral position (*see* fig. 7). The eye position turnaround point was taken as the first movement into the compensatory direction (dashed line in fig. 7). Dominant time constants calculated from the frequency at a 45 deg phase advance are indicated.

This animal had been previously trained to perform pursuit movements. From fig. 11 it is apparent that the eyes could reach velocities during pursuit surpassing those of the saccades. The animal could hold eccentric positions during fixation and could execute normal pursuit movements at least around ± 20 deg of primary position.

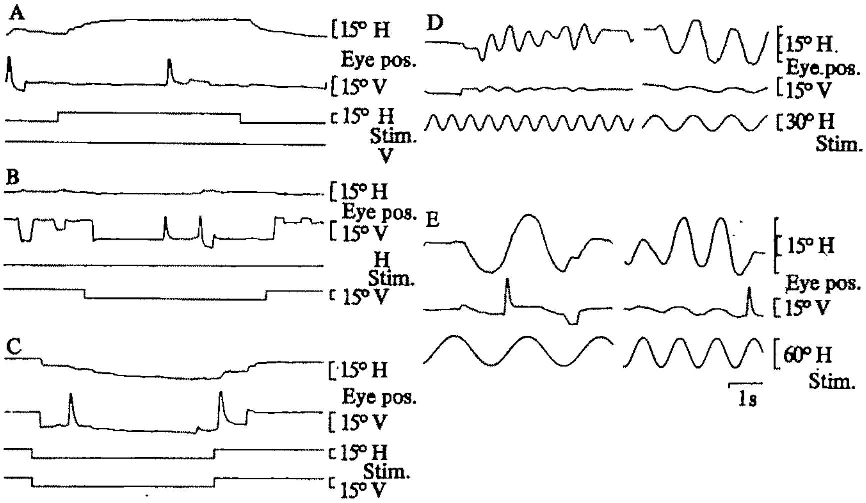

FIG. 11. Animal H69 with a small bilateral rostral PPRF lesion was trained to perform goal-directed saccades (*left side* of the fig.) or pursuit movements (*right side* of the fig.). Stimulus light position is shown below eye position trace. In A, during a step displacement to the right, the animal is finally able to bring the eyes on target with a succession of small saccades. In the reverse direction there is one continuous slow movement over 2 s. In B, there are normal target saccades in the vertical direction. In C, the target is displaced in an oblique direction. It takes considerably longer to bring the eyes on target in the horizontal than in the vertical direction. A large vertical displacement or a blink actually helps to shift the eyes in a horizontal direction. D and E are horizontal pursuit movements, in which the animal far exceeds velocities obtained in A during step displacements.

DISCUSSION

In the current study lesions were placed in the brainstems of monkeys in an attempt to elucidate structure function correlations pertaining to eye movement disorders, especially gaze palsies found clinically. The novel technique in this study is the prior identification of areas with single unit recordings, and the use of kainic acid injected locally to destroy mainly the cells in a particular region of the brainstem while sparing fibres of passage.

With kainic acid lesions we were able to reproduce clinically encountered brainstem syndromes, and to obtain additional information about eye movement deficits. In clinical cases such isolated lesions are rare, or eye movement recordings cannot be obtained in conjunction with post-mortem findings, eliminating the possibility of a causal analysis. Especially with bilateral lesions, patients are often in such poor general condition that extensive testing cannot be undertaken.

Morphology of Kainic Acid Lesions

Light microscopic examination of kainic acid lesions showed a virtually complete loss of neuronal cell bodies with preservation of fibres of passage. This is in accordance with previous reports (Coyle *et al.*, 1978; McGeer *et al.*, 1978). In our study, however, higher concentrations of kainic acid were required to induce clinical deficits in the oculomotor system of monkeys than were necessary to cause intrastriatal lesions in rats. This possibly reflects a reduced number of kainic acid binding sites in the pons as compared to the striatum, as indicated by kainic acid binding studies in different species (Henke and Cuénod, 1980). With the relatively high concentrations of kainic acid used in this study, although some damage to myelinated fibres was induced, many fibres of passage remained intact. Specifically with caudal PPRF lesions, abducens rootlets appeared normal in a myelin stain preparation; during horizontal VOR testing, both eyes deviated over the full range with equal velocity, indicating normal function.

Only one brain was processed for electron microscopy. It confirmed the findings of the myelin stains observed by light microscopy. There were many fibres of normal appearance, but an exact fibre count was not considered essential for this study.

Experimental Gaze Palsies

Unilateral PPRF lesions. Eye movement deficits after unilateral lesions of the PPRF in monkeys have been fully described (Bender and Shanzer, 1964; Cohen *et al.*, 1968). Subsequently we have extended this work to recording single neuron activity in other unaffected regions to study the altered information processing (Jaeger *et al.*, 1981). In brief, in the contralateral PPRF, activity still precisely reflected the occurrence of eye movements. For example, strong correlations existed between vector components of a movement and parameters of single neuron activity. Unit activity was always accompanied by an eye movement. In particular, pause neurons exhibited their pauses only when eye movements actually occurred, which was possible only into the contralateral side or in a vertical direction.

Single neuron recordings in the vestibular nuclei showed that all rapid eye movement information towards the ipsilateral side was absent, while that for movements in other directions was still present. During vestibular or optokinetic nystagmus, neurons exhibited the typical tonic increase or decrease of activity. In the normal monkey, the firing pattern of about 50 per cent of vestibular nuclei neurons is also modulated with rapid eye movements. This modulation was still present for movements towards the contralateral side or in the vertical direction. During any stimulation which would have resulted in nystagmus towards the ipsilateral side in a normal monkey, neurons displayed only a tonic frequency change with a conspicuous absence of any nystagmic modulation.

An important result of the unilateral kainic acid lesions was that the deficits are identical to those of previous electrolytic lesions. The earlier interpretations can therefore be fully confirmed: there are cells in the PPRF which are responsible for generating rapid eye movements in the horizontal plane towards the ipsilateral side. After destruction of these cells, there is no activity which could be interpreted as a 'desired but unexecuted motor command' to the ipsilateral side in other structures of the brainstem such as the contralateral PPRF or the vestibular nuclei.

Bilateral PPRF lesions. These gave two basic results. (1) Bilateral caudal lesions lead to a disruption of rapid eye movement generation in all directions, and (2) bilateral rostral lesions lead to a loss of rapid eye movements only in the horizontal direction. An immediate deduction is that there must be functional subdivisions of the PPRF. Single neuron recordings, as described in the Introduction, support such subdivisions. There is a concentration of pause neurons in the mediocaudal part of the PPRF. Their possible coordinating and trigger roles have been discussed (Keller, 1977; Raybourn and Keller, 1977).

The rostral PPRF contains mainly long-lead burst neurons with ipsilateral on-directions (Hepp and Henn, 1983). Neurons fire maximally for movements of specific amplitudes and directions; they are similar to neurons found in the superior colliculi (Wurtz and Goldberg, 1972; Mohler and Wurtz, 1976; Mays and Sparks, 1980). Our results demonstrate that bilateral destruction of these cells in the rostral PPRF leads to a loss of all rapid eye movements in the horizontal plane with only a slight reduction in the velocity of vertical eye movements. Animals can also fixate their eyes in various vertical positions. Although rapid eye movements are lost, pursuit movements in the horizontal plane appear normal (animal H69). This emphasizes the dichotomy in the generation of visually evoked slow and fast movements. In our example the velocity of horizontal pursuit reached much higher values than eye movements in response to sudden target displacements.

We can deduce that at this premotor stage, horizontal and vertical rapid eye movement generation is separate. The parametric elaboration of vertical eye movements therefore has to be localized to cells in the rostral iMLF (Büttner-Ennever *et al.*, 1982).

Bilateral caudal PPRF lesions lead to a total disruption of rapid eye movement generation in all directions. Similar results with electrolytic lesions was mentioned by Bender and Shanzer (1964), but have not been fully documented. The deficit in rapid eye movement generation can be explained by the activity patterns of the neurons which are lost. An intermediate stage of information processing linking the rostral PPRF to the motoneurons as final common pathways is lost. No rapid eye movements can therefore be generated in the horizontal plane. The additional destruction of pause cells in the medial PPRF leads to a loss of the coordinating and timing mechanisms. Neurons in the rostral iMLF, although they supposedly receive an independent parametric input for vertical movements, process this information in such an asynchronous way that the eyes can neither be held stationary in a fixation period nor can they be moved with maximal velocity and high precision as during a rapid eye movement. Some exploratory single neuron recordings in the rostral iMLF in two animals tend to support these considerations.

In all animals, with both unilateral and bilateral lesions, the velocity-to-position integrator was intact. Activity in the PPRF relates only to parameters of rapid movements. However, the eyes have to be held in the new position after the movement. This requires a new set of innervation for the extraocular muscles which is reflected in their different degree of tonic activity during fixation periods. This process of obtaining position information out of a velocity signal is, in mathematical terms, an integration.

It was especially clear in bilateral lesions that this integration process was intact. The eyes could be held in eccentric positions. Also, during vestibular testing, the eyes made fully compensatory movements during step displacements as well as during rotation with sinusoidal velocity profiles. In the vestibular system, over a wide range, information about head motion is coded in terms of a velocity signal. Again, this signal has to be integrated to excite ocular motoneurons with the appropriate firing frequency to move and hold the eyes. Any deficit in this integrator would easily be seen in a phase shift between turntable and eye position, which was not the case. These considerations exclude the PPRF as a site for such a velocity-to-position integrator. Its location remains unknown. By exclusion, the nucleus prepositus hypoglossi is a possible candidate. It is also conceivable that neuronal networks, not confined to one restricted area, are responsible for this process.

Human Pathology

Unilateral pontine lesions with loss of rapid eye movements towards the ipsilateral side were described in the last century (Bleuler, 1885). Several reviews summarize the clinical literature (Freeman, 1922; Crosby, 1953; Bender, 1980; Henn and Büttner, 1982). These clinically observed deficits were the starting point for all animal experiments. Deficits in human eye movements after pontine lesions are identical to those in monkeys. In the human cases the cause is often a large destructive lesion. Additional deficits are therefore frequently encountered, but are not consistently present. These include abducens palsy, facial palsy, and loss of the vestibulo-ocular reflex (Holmes, 1921, 1931; Freeman *et al.*, 1943; Jung and Kornhuber, 1964; Hoyt and Daroff, 1971; Pierrot-Deseilligny *et al.*, 1981, 1982).

Bilateral pontine lesions are exceedingly rare or patients are so severely ill or comatose that they cannot be appropriately tested. There are a few reports of bilateral lesions with global gaze palsy, sometimes only transient (Hoyt and Daroff, 1971; Christoff, 1974). One recently described patient had a documented lesion restricted to the pons (Larmande *et al.*, 1982). This patient, besides her total horizontal gaze palsy, had slowing of saccades in the vertical direction, absent vestibular responses, slow deviations only during OKN without rapid phases, but normal vertical pursuit movements. Another case had a bilateral metastatic tumour in the pons with preservation of vertical movements (Pierrot-Deseilligny *et al.*, 1984). We recently observed a patient with an acquired bilateral horizontal gaze palsy with intact vertical rapid and command movements on clinical testing. The patient was too ill for more formal quantitative testing. In summary, clinical cases with bilateral pontine lesions are inconclusive. Our hypothesis would offer an explanation for the fact that in some cases vertical eye movements have been found to be normal and in others affected.

A familial disorder with congenital absence of all horizontal eye movements, but intact vertical movements, has been described by several authors (*see* recent review by Vetterli and Henn, 1981). It is usually combined with bony abnormalities of the spine such as kyphoscoliosis or fused vertebrae. No autopsies on these cases are known and its neuropathology remains uncertain.

Chemical Lesions vs Structural Lesions

Kainic acid or electrolytic lesions of the caudal PPRF lead to identical deficits in eye movements. This proves that the symptoms are the result of cell loss in this region and not damage to fibre systems.

There seems to be no clinical syndrome which leads to an isolated cell loss in the PPRF. Several cases of congenital bilateral horizontal gaze palsies have been documented, but these are developmental disorders, with no available neuropathology. There are some degenerative diseases of unknown aetiology which exhibit cell loss in the PPRF in the context of a diffuse widespread cell loss such as progressive supranuclear palsy. However, the more common focal lesions encountered clinically are destructive. Structures in the immediate vicinity are therefore usually also involved. These include the abducens nucleus, the internal genu of the facial nerve, and vestibular projections in the MLF. The VOR is therefore often lost (Daroff, 1982). However, as small electrolytic lesions have shown, unilateral caudal lesions are possible with an intact VOR (Jaeger *et al.*, 1981). The loss of the VOR might thus be a frequent sign of caudal PPRF lesions, but it cannot be considered to be obligatory.

One of our specific questions in undertaking this study was whether bilateral pontine lesions simply duplicate the symptoms of unilateral lesions or in addition lead to defects in vertical gaze. Surprisingly, we found that bilateral rostral lesions lead to a duplication of deficits, while caudal lesions lead to additional deficits of vertical gaze.

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THE ANKLE STRETCH REFLEXES IN NORMAL AND SPASTIC SUBJECTS

THE RESPONSE TO SINUSOIDAL MOVEMENT

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SUMMARY

Forces and electromyograms were recorded during sinusoidal flexion-extension movements of normal and spastic ankle joints. Spastic subjects showed relatively stereotyped responses, with evidence of a vigorous spinal stretch reflex. The responses of normal limbs were variable; there was little reflex response to the first cycles, but as the movement continued the reflex responses increased and often came to resemble the responses of spastic limbs.

At some frequency between 3 and 7 Hz, the reflex response was so timed that it tended to assist rather than resist the movement; this was the frequency at which many subjects (normal, as well as spastic) exhibited spontaneous clonus if an appropriate load was attached to the foot. The frequency of this clonus changed with changes of load.

It is concluded that whereas the gain of a normal stretch reflex may vary considerably, the stretch reflex of the spastic subject is set at one end of the normal range. With this high gain, the stretch reflex may support spontaneous clonus in both normal and spastic subjects.

INTRODUCTION

Previous papers (Evans *et al.*, 1983; Rack *et al.*, 1983) described responses of normal human ankle joints to imposed flexion-extension movements. In this paper we describe the responses of patients with spastic paresis, and compare them with the normals. A similar method has been used by Herman *et al.* (1973) and Freedman and Herman (1975).

Each cycle of an imposed sinusoidal movement is met by a corresponding cyclically changing force. Some part of this resisting force is due to the mass of the foot, but this part may be computed and subtracted from the total; most of what remains is the force which the muscles exert on the joint. Only a part of this muscle force arises from reflex activity, but by examining the responses to different frequencies of movement, and choosing appropriate methods of display, a useful

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picture of the magnitude and timing of these reflex responses to the movement can be obtained (Brown *et al.*, 1982*a*).

When the responses of normal limbs were analysed in this way, it was clear that there were wide differences between the reflex responses of the same subject on different occasions (Rack *et al.*, 1983). During the course of an experiment the reflex responses often increased very considerably so that after some minutes of continuous movement there might be much more reflex activity than at the outset. We are thus unable to use the normal subject as a simple baseline from which to assess the responses of spastic joints; indeed, it now seems more appropriate to regard the reflexes of these patients as being fixed in a 'hard on' state, which is not essentially different from a state that normal subjects may sometimes achieve.

Ankle clonus has for many years been regarded as a spontaneous oscillation of the stretch reflex. Recently, however, it has been suggested that clonus arises from the action of a central oscillator within the spinal cord, and that the stretch reflex pathway plays no part (Walsh, 1976), or only a limited part (Dimitrijevic *et al.*, 1978, 1980). Some of the movements which were used in this investigation were similar in frequency to the movements of spontaneous clonus. The responses to these movements, taken together with records of clonus in the same subjects, provide a convincing demonstration that clonus is indeed the self-sustaining oscillation of a stretch reflex pathway.

METHODS

Experiments were performed on 17 patients with spastic lower limbs. Subjects were selected in whom the ankle tendon jerk was exaggerated, and many of them exhibited spontaneous clonus. They ranged in age from 10 to 76 years; 15 were male, 2 female. Nine subjects were hemiparetic after cerebral vascular lesions, 7 suffered from multiple sclerosis, and 1 from motor neuron disease. All had severe weakness at the ankle, and many had no voluntary movement at the joint. All received regular physiotherapy, and a good range of passive movements of the joint was possible without pain. The responses of these spastic subjects were compared with 13 normal subjects. All experiments were undertaken with the informed consent of the subject.

The investigation involved two different types of experiment: sinusoidal driving of the joint was performed on all the spastic subjects, and measurements of spontaneous clonus were made on 8.

Imposed Sinusoidal Movements

The method has already been described in detail (Evans *et al.*, 1983). Briefly, the seated subject had his foot in a mould which was mounted in a way that permitted only flexion-extension movements at the ankle joint; the knee was held immobile. By means of a motor and crank mechanism, the foot was driven through sinusoidal flexion-extension movements at a variety of amplitudes and frequencies. The limb position and the resulting force were recorded on magnetic tape along with EMG signals from soleus and tibialis anterior. Particular care was taken to hold the foot securely in the mould, and to confine the movement to the ankle joint. Electromyograms were recorded through pairs of silver cup electrodes placed on the skin over the muscles. The signals were amplified by an Isleworth A101 pre-amplifier which, together with its optical isolator, had a band pass of 65 Hz to 5 kHz. With the gains used there was no detectable movement artefact from the recording leads, and when the motor units were silent we could detect no signal phase-locked to the movement.

The components of the driving force which were required to move the mould and the mass of the foot were of little interest; these were therefore computed for each frequency of movement (*see* Evans *et al.*, 1983) and subtracted from the total. What then remained were the forces acting at the joint, and it is these forces that are displayed in the figures (*see* fig. 1). It was often useful to average responses to a number of cycles of similar frequency (fig. 2); before averaging the EMG signals were rectified.

The relationship between movement and force was also displayed by a third method. At each frequency of movement the force was divided by the movement to give a stiffness vector (fig. 5); the amplitude of this vector indicates the resistance to movement (torque/angle) and its phase indicates the amount by which the force leads or lags the movement. The methods of analysis have already been described in detail (Brown *et al.*, 1982*a*, *b*).

In most of the experiments the subject was instructed to make no effort of any kind, and to relax the ankle as far as he was able (occasionally a subject fell asleep during the experiment). The ankle was then driven through sinusoidal movements at a number of different frequencies. Usually we increased or decreased the frequency in a continuous sweep, but on some occasions, separate samples of record were made at constant frequencies. The results obtained from spastic subjects were similar whichever method was used.

Normal subjects were sometimes asked to exert a steady mean plantarflexing force while the movement proceeded. We then displayed the mean force to them on a meter of long time-constant, with instructions to keep the pointer at some predetermined setting.

Clonus Measurements

With the ankle and knee held in the moulds described above (*see* fig. 7), a variety of different springs and masses were attached to the foot. A fuller description appears under Results and in the figure legend.

RESULTS

Imposed Sinusoidal Movement

Figs. 1 and 2 illustrate the responses of one of our spastic subjects to a single sequence of sinusoidal movements at frequencies that progressively increased from 3 Hz. The subject had no voluntary power at the ankle but the joint was freely mobile, and the plantar surface of the foot could be dorsiflexed to an angle of 90 deg with the anterior border of the tibia by minimal force. Each sample of record in fig. 1 shows the soleus EMG (*above*) and forces (*middle*) when the foot was moved through ± 2.3 deg around this 90 deg position (*lowest record*).

Clear bursts of EMG activity were locked to the imposed movement; at 3 to 5 Hz the EMG burst occurred during the later part of each dorsiflexing movement, but as the frequency increased the bursts increased in amplitude and moved later, so that at 6.5 Hz the EMG burst corresponded to the position of maximal dorsiflexion. At the higher frequencies, however, the EMG bursts occurred only in alternate cycles. Similar resuls were reported by Freedman and Herman (1975).

These effects of frequency on the electromyogram can be seen more clearly when the signals are rectified and averaged over a number of cycles. This has been done in fig. 2, where the whole sequence of 386 cycles has been divided into 0.5 Hz bins; within each bin the EMGs of all the successive pairs of cycles have been averaged to give the responses shown in fig. 2A.

The figure shows the forces that acted on the joint (after subtraction of forces required to move the apparatus and the mass of the foot). The force fluctuated in characteristic ways, but the fluctuations were often far from sinusoidal, and the relationship between soleus EMG and the plantarflexing force was not always obvious. The force records can, however, be explained if account is taken of interactions between the periodic muscle activity (as judged from the EMG) and the direct mechanical effects of the imposed movement. When the frequency of movement was low (the 3.5 Hz records of figs. 1 and 2), each burst of EMG activity was followed by a peak of force which resembled a simple muscle twitch, and this rise in force was then enhanced by the fact that the muscles were lengthening (Abbott and Aubert, 1952). It was evident that at this frequency each extension of the calf muscles led to a reflex force which resisted *that same extension movement.*

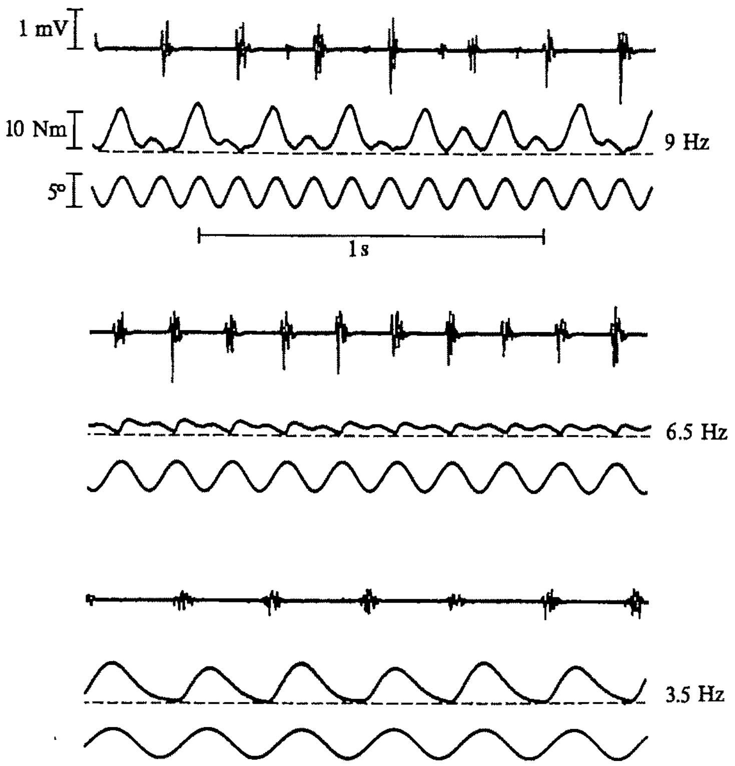


FIG. 1. Three samples of record obtained during movement of the left ankle of a spastic subject through ± 2.3 deg. Each sample shows the soleus EMG *above* and the joint position *below* (dorsiflexion upward). The *middle* trace shows the forces that acted at the ankle joint (the forces required to move the apparatus and the mass of the foot have been subtracted from the original data), and the broken line indicates the force zero (recorded before the foot was placed in the mould). The subject was a 60-year-old man with a spastic left hemiplegia following a cerebral vascular lesion five months earlier.

As the frequency of movement was increased to 5 or 6 Hz (fig. 2) and the cycle time correspondingly diminished, the EMG bursts moved later in the cycle, as would be expected of a delayed response to the movement. At these frequencies the associated force peaks occurred after maximum dorsiflexion, when the plantarflexing movement had already begun. The force peaks were then smaller, even though the EMG bursts were particularly large, and this decrease in force was, presumably, a reflection of the fact that muscles generate smaller forces when they are shortening.

At frequencies of 6 Hz or more, some of the effect of each muscle activation persisted into the subsequent lengthening movement, and often led to a second force peak as the calf muscles were re-extended. In a limited frequency range there were thus two distinct peaks in the force records (figs. 1 and 2, 6.5 Hz), one of which occurred soon after the EMG activity while the other accompanied the subsequent lengthening movement. As the frequency was further increased, it was only the later peak that persisted (fig. 2, > 7 Hz). The reflex response to each extension of the calf muscles was then a resistance to *the next extension movement.*

In the transition from 5 Hz to 7 Hz, the main effect of the stretch reflex thus moved forward by nearly a whole cycle, so that whereas at 5 Hz the reflex acted to resist the extension movement which had initiated it, at 7 Hz the reflex effect was on the lengthening phase of the succeeding cycle. At an intermediate frequency (6.5 Hz in figs. 1 and 2), the reflex force was so timed that it actually reduced the resistance to

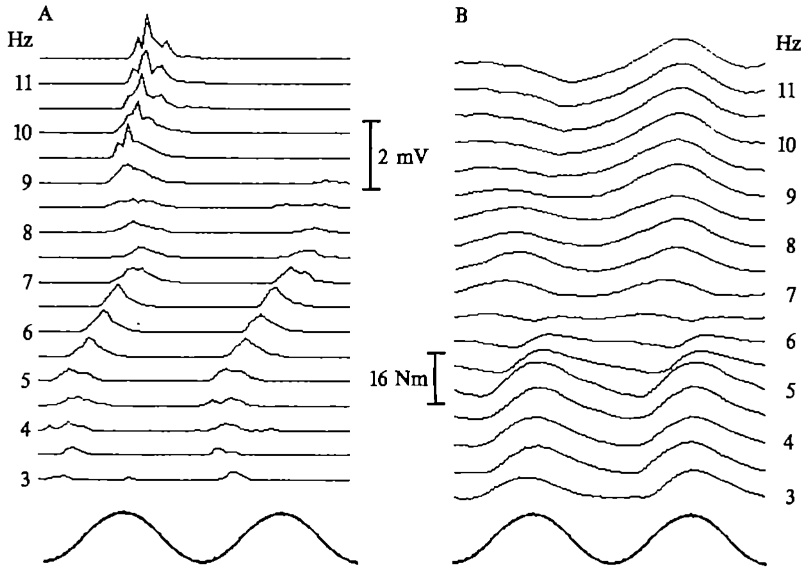


FIG. 2. Responses to movements of progressively increasing frequency. EMG (on the *left* of the figure), and force records (on the *right*) from 386 consecutive cycles were collected into 0.5 Hz bins (the 7 Hz bin thus included all cycles at frequencies between 6.75 and 7.25 Hz). Within each bin, the forces and rectified EMGs of successive pairs of cycles were averaged. The *lowest* trace on each side shows the joint movement. Records from the same experiment were used in fig. 1.

movement, and the force response to the sinusoidal movement remained relatively flat. In this intermediate frequency range the low resistance to movement was accompanied by very clear peaks of EMG activity (fig. 2).

As the frequency of movement was still further increased to 9 Hz or more, the EMG activity became confined to alternate cycles. This alternation of the reflex response can also be seen in the force records; the large EMG response to one cycle of movement then gave rise to a large force in the *next* cycle.

The responses of normal subjects. The responses of normal subjects to these same movements were much more variable. Different subjects have different amounts of reflex activity, and even the responses of the same subject change considerably from time to time. Further changes are seen when the subject exerts a voluntary force against the machine. These normal responses have already been described in detail (Evans *et al.*, 1983; Rack *et al.*, 1983), so we shall describe them quite briefly here.

When a normal subject sits with his leg relaxed, and makes no attempt to assist or resist, there is seldom a detectable reflex response to the smaller or slower movements. As the frequency increases, however, electromyograms of the calf muscles may show intermittent activity whose timing is locked to the movement. At the beginning of an experiment, the amount of this activity is often small, and it may involve only a few motor units. The subject of fig. 3A was one who had active tendon jerks, but in that figure a movement through ± 2.3 deg at 4.5 Hz (*lowest record*) provoked no detectable EMG response, although at 8 Hz or more, bursts of activity did appear in each cycle. Many of our subjects showed less EMG response than in fig. 3A, and some showed none at all. There are small sinusoidal force fluctuations in fig. 3A, but these are little more than would be expected from a limb with completely passive muscles (Evans *et al.*, 1983). There are none of the irregularities that appeared in the force records of spastic joints (fig. 1).

Fig. 3A illustrates the response to the first cycles of sinusoidal movement. When the same movement was continued for a number of minutes, the situation changed. There was then a much more vigorous reflex response to movements at all frequencies, and even smaller or slower movements might be accompanied by visible bursts in the electromyogram (Evans, *et al.*, 1983). Fig. 3B was also obtained from a normal subject, but after he had already undergone about 30 min of testing, including thousands of cycles of sinusoidal driving. The movement was the same as for fig. 3A, and again the subject was instructed to relax; however, the EMG records of fig. 3B show that his calf muscles were active during each cycle, even when the frequency was low. He was unable to prevent this activity (note different EMG scales).

In fig. 3B the forces are larger than in fig. 3A, and the force waveforms altered with changing frequency; the records were in many respects similar to those obtained from spastic subjects (fig. 1). At the low frequency each burst of EMG activity was followed by a steep rise in force, whereas at an intermediate frequency the effect of the reflex tended to reduce the force fluctuations, and at high frequencies the EMG and force were concentrated into the alternate cycles. Figs. 4A and B show data from the same experiments as fig. 3, but displayed in the same way as fig. 2. A comparison of figs. 4A and B confirms the differences between these two sets of normal records.

If, while the movement continued, the subject was instructed to exert a mean plantarflexing force (10 to 20 per cent maximal), there was a further increase in the amount of reflex activity (*cf* Marsden *et al.*, 1972). During sinusoidal movements this appeared as a further modulation of the EMG and force records (fig. 4C).

A comparison of the normal responses of figs. 4B and C with the responses of a spastic subject (fig. 4D) confirms that under appropriate conditions, most of the features of the spastic stretch reflex might appear in the normal subject. In each of these figures the amplitude and timing of EMG records changed with frequency in a similar way, and the same rather complex pattern of changes was seen in the force records. It should, however, be noted that the actual frequencies at which these various changes occurred were not identical.

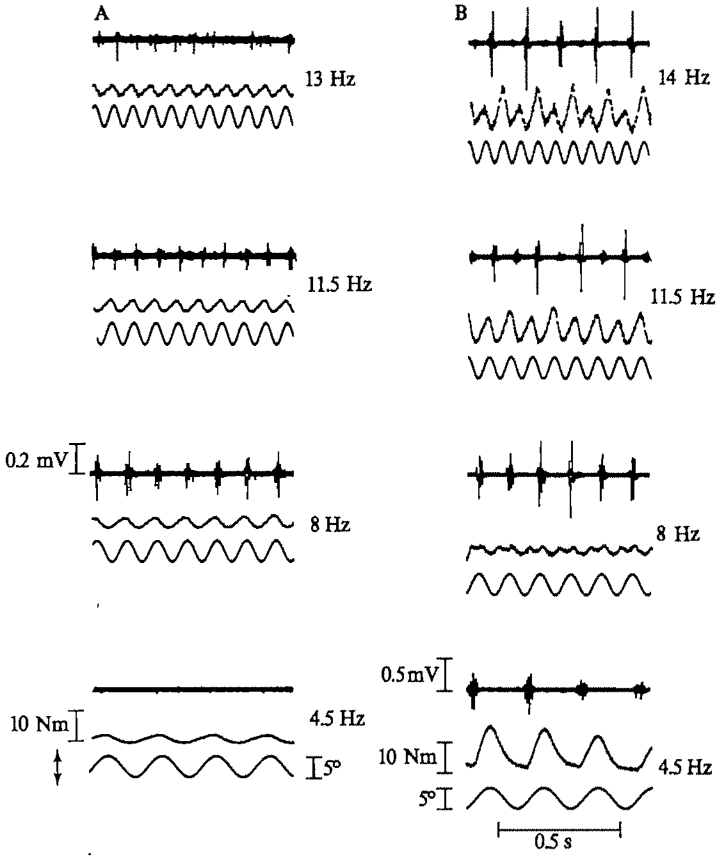


FIG. 3. Responses of normal ankle joints displayed in the same way as in fig. 1. A, records obtained at the beginning of an experiment. B, records obtained after a subject had undergone 30 min of continuous sinusoidal movement. Amplitude of movement ± 2.3 deg.

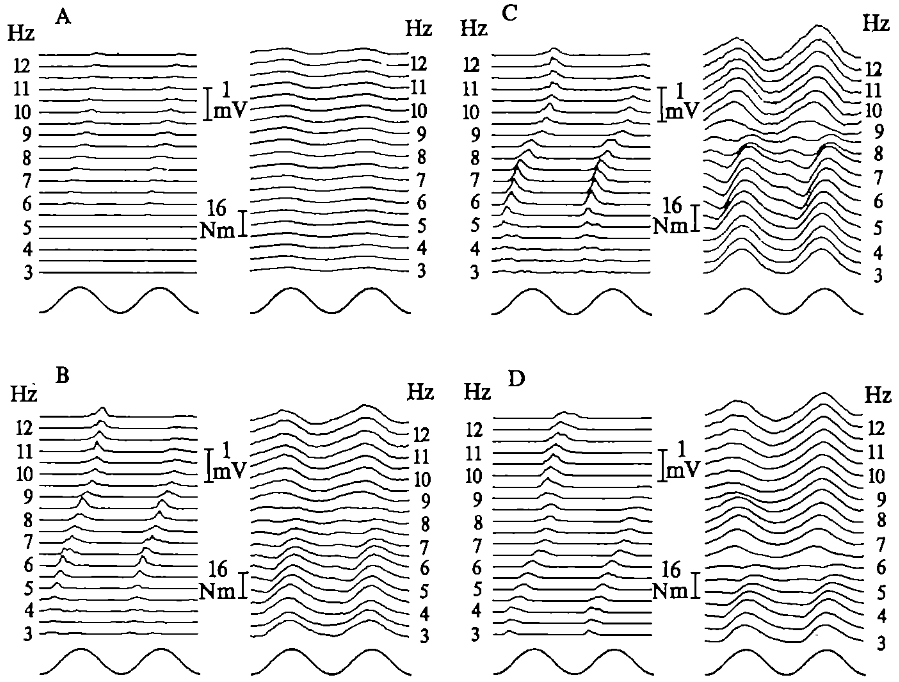


FIG. 4. Four sets of data displayed as in fig. 2. A, B and C are from normal subjects. A and B correspond to figs. 3A and B. They show the responses of normal subjects at the beginning of an experiment, and after 30 min of driving. For C, the subject exerted a continuous plantarflexing force (10 Nm). D shows records from a 61-year-old man with an eighteen month history of a spastic left hemiplegia following a cerebral vascular lesion. Amplitude of movement ± 2.3 deg.

Vector representations of force. It was often convenient to represent resistance to sinusoidal movement as a vector (*see* Brown *et al.*, 1982*a*). This method displays only the amplitude and timing of that component of force which has the same frequency as the movement. Fig. 5 shows plots of force vectors obtained from six different experimental runs. Figs. 5A to D are from the same data as figs. 4A to D. Figs. 5E and F are from other subjects with spastic weakness of the ankle joint.

Each point in fig. 5 represents the resistance to movements in a particular frequency range. Thus, in fig. 5C, the 5.5 Hz point represents the amplitude and phase of a sinusoid which would be the best fit to the 5.5 Hz force record in fig. 4C. The distance of this point from the origin of the plot represents the amplitude of that sinusoid, while its angular separation ϕ from the horizontal axis indicates the phase relationship between this fitted force sinusoid and the joint position. This particular point indicates a sinusoidal force that fluctuated through ± 8 Nm (200 Nm/radian of movement), the peak plantarflexing force occurring 10 deg (5 ms) after the joint was most dorsiflexed. By contrast, the 8 Hz point in that same figure indicated a force sinusoid of amplitude only ± 2.5 Nm (60 Nm/rad), which lagged behind the

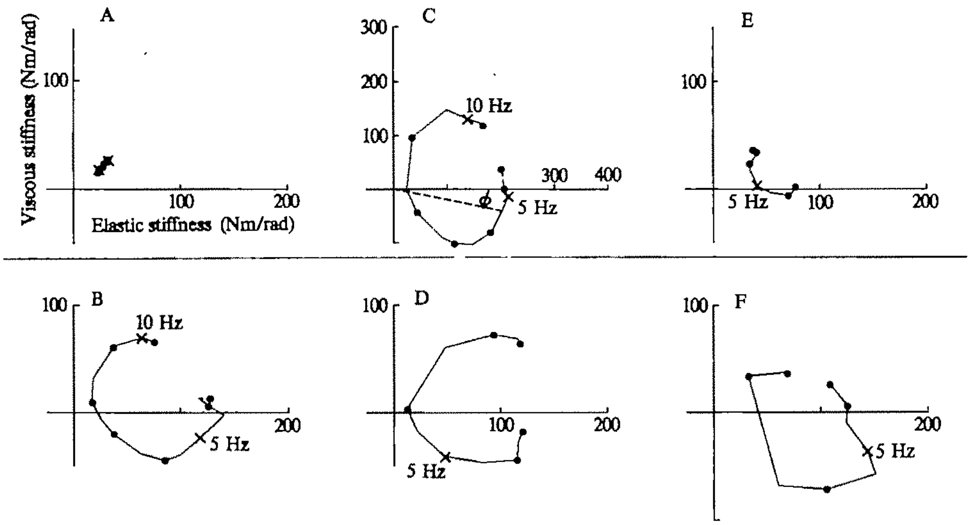


FIG. 5. Effect of frequency on the joint stiffness vectors. Each part of the figure represents the responses to a frequency sweep and each point represents the average force in a 0.5 Hz frequency bin. The distance of a point from the origin (dotted line in C) denotes the amplitude of the component of force at the movement frequency, while its angular displacement ϕ from the horizontal axis indicates the phase lag of that force on the movement. A to D are from the same data as fig. 4A to D; E and F are from other spastic subjects. The subject of E was a 54-year-old man suffering from motor neuron disease. (Amplitude of movement was ± 2 deg.) The subject of F was a 16-year-old boy with multiple sclerosis. (Amplitude of movement was ± 1.4 deg.)

movement by 48 deg (25 ms). Points that lie on the horizontal axis indicate a resistance that was entirely elastic; when points lay on the vertical axis, they indicated a viscous (frictional) resistance.

The normal subject met the first cycles of movement with a relatively small force (± 30–45 Nm/rad in fig. 5A), and the timing of this force hardly changed with alterations in frequency. It was always a positive resistance to the movement, that is, a dorsiflexing movement was met by a plantarflexing force which reached its maximum in advance of the peak displacement and while the movement was still continuing.

In spastic subjects (figs. 5 D–F) and in the normal who had already undergone a number of cycles of driving (figs. 5B and C), the force vectors changed with frequency in a characteristic way. As the frequency increased, the vectors moved in a clockwise direction round a C-shaped path; this is a response that is expected when each cycle of movement generates a corresponding force, but a significant part of that force appears after a delay. As the frequency of movement increases, the delay becomes a larger fraction of the cycle time, with a consequent displacement of the force vector. The size, shape and position of the C then give useful information about the amplitude of the reflex activity, about its timing, and about its possible effects on the behaviour of the joint. The interpretation of these vector paths is considered in more detail elsewhere (Rack, 1981*a*; Brown *et al.*, 1982*a* to *d*). For our present purposes it is sufficient to draw attention to two points. (1) The size of the C-shaped path gives an indication of the amount of reflex activity. (2) When, at some frequency of movement the vector lies below the horizontal axis, then in each cycle the force is so timed that it *assists* rather than *resists* the movement.

In each of these three spastic subjects (figs. 5 D to F) the force vectors followed a C-shaped path. The size of the C varied from subject to subject, but the response had this same form from the beginning of the experiment, even though they were trying to relax the limb. The force vectors of normal limbs sometimes also described a circular path, but only after a preliminary period of sinusoidal driving; under those circumstances the responses of the normal and abnormal limbs became very similar.

Activity in antagonist muscles. Although electrodes were placed over the tibialis anterior of many of our subjects, it was often impossible to detect any activity in that muscle, and activity from the much larger calf muscles appeared at those electrodes. There were, however, some occasions when the tibialis anterior of the spastic subjects did respond to the imposed movement with vigorous bursts of EMG activity. In the subject of fig. 6 we had already recorded a number of sequences of sinusoidal movement of smaller amplitudes and seen reflex activity in soleus, but without evidence of activity in tibialis anterior. When the amplitude was increased to ± 2.3 deg, the tibialis also became active, with bursts of EMG activity which were

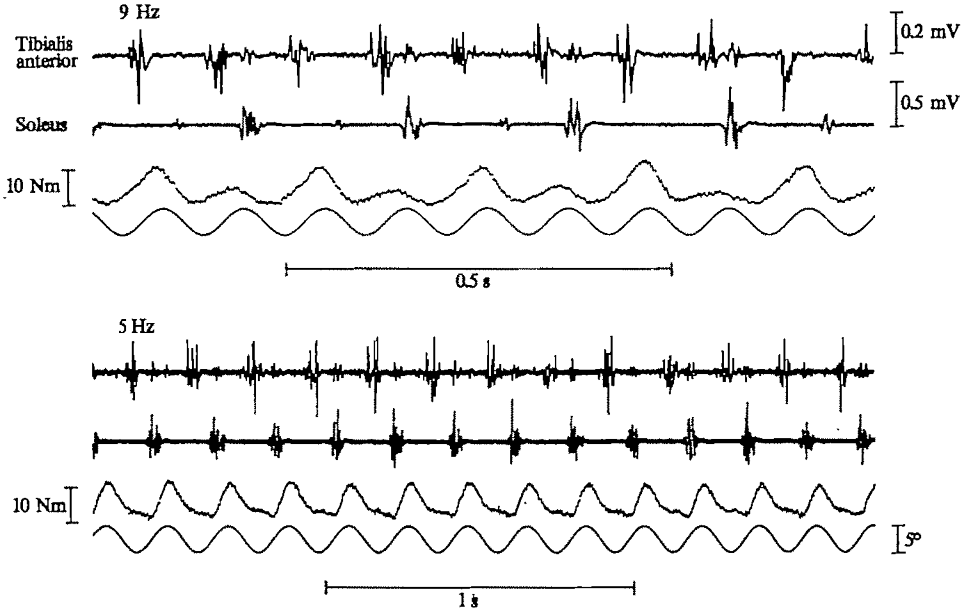


FIG. 6. Activity in antagonist muscles of a spastic subject. The responses to movements of ± 2.3 deg are displayed as in fig. 1, but with EMG recordings from both tibialis anterior and soleus. From a 60-year-old man with a hemiparesis following a cerebral vascular lesion eighteen months previously.

locked to the movement, but clearly out of phase with the signals from the soleus (5 Hz record of fig. 6). This activity came and went in a capricious manner without having any detectable effect on the force records. When tibialis anterior was active during movements at frequencies of 8 to 12 Hz (the 9 Hz record of fig. 6), the EMG activity was often present in every cycle, even though the soleus activity was confined to alternate cycles.

The force fluctuations which accompanied sinusoidal movements were always increases in the plantarflexing force above the resting level, and this was true whether or not tibialis anterior was active. It was presumed that the forces generated by tibialis anterior were always small compared with those from the much larger calf muscles.

The timing of the reflex response. In the preceding paragraphs we have emphasized the similarity between spastic patients and the normal subjects who had undergone prolonged sinusoidal driving. There were, however, some differences. During the higher frequency movements the reflex activity was often confined to alternate cycles. In normal subjects this seldom occurred below 9.5 Hz, whereas in the spastic patients it was seen at 7 or 8 Hz, and sometimes as low as 6 Hz.

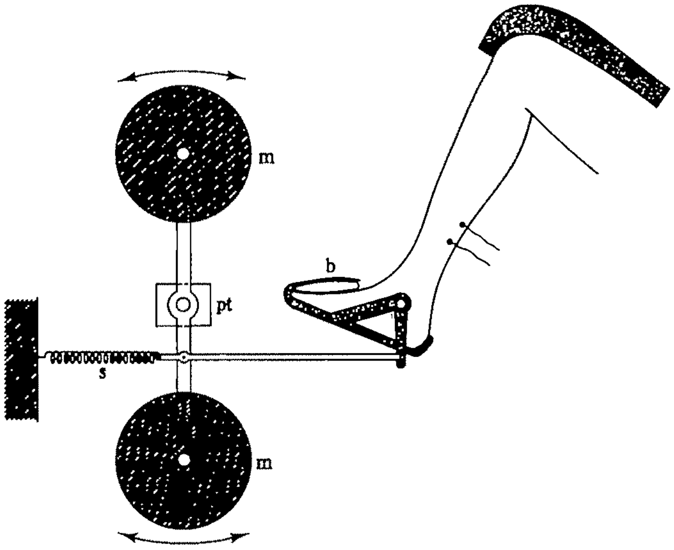
The frequency of movement at which reflex activity was so timed that it reduced force changes to a minimum was also lower in the spastic than in the normal subjects; in figs. 2 and 4D it was with a movement at 6 or 6.5 Hz that the reflex reduced the resistance to a minimum, whereas in the normal subject (figs. 4B and C) this same reduction in resistance occurred at 8.5 Hz. This can also be seen in the vector plots of fig. 5 where the frequency points are distributed round the C-shaped path in rather different ways. In the spastic patients (fig. 5D to E), it is at some frequency between 5 and 7 Hz that the points lie closest to the origin whereas in the normal subject (figs. 5B and C) it is the 8 and 8.5 Hz points that lie in a similar position. These results indicated that in a frequency range of 6 to 8 Hz, the spastic subjects had a longer than normal delay in the neural pathway between the movement of the muscle and the resulting reflex EMG or force.

Before reaching the conclusions of the preceding paragraph, some complicating factors had to be considered. The timing of the normal stretch reflex response to sinusoidal movements depends on their amplitudes, and may alter considerably when very small movements are used (Rack *et al.*, 1983). Comparisons of normal and spastic responses were therefore confined to movements of ± 2 deg or more.

The muscle fibres and muscle spindles do not necessarily move with the same amplitude and time course as the ankle joint, because the Achilles tendon is a relatively compliant coupling in which some of the movement may be 'lost' (Rack *et al.*, 1983). Nevertheless, the tendon length will only change if the force changes, so that a number of complications can be avoided by concentrating on those experimental conditions in which the force fluctuation was small (the stiffness vectors lay close to the origin).

When we used movements of ± 2 deg or more, this minimal force fluctuation occurred when the EMG burst coincided with maximal dorsiflexion, and this was true both for normal and spastic limbs. Since this situation occurred at lower frequencies in the spastic than in the normal subjects, the interval between muscle spindle movement and the consequent EMG activity must have been longer in the spastic subjects.

FIG. 7. The apparatus used for study of clonus. The knee and foot were fixed in the moulds used during sinusoidal driving, the forepart of the foot being held in place by an inflated bag (b). The foot mould was free to move, but could only do so by lengthening or shortening the spring (s), and by moving the lever arm and the masses (m). Movement was recorded through an *Asynn* angular position transducer (pt) (Smith). Cutaneous EMG electrodes were fixed over soleus.



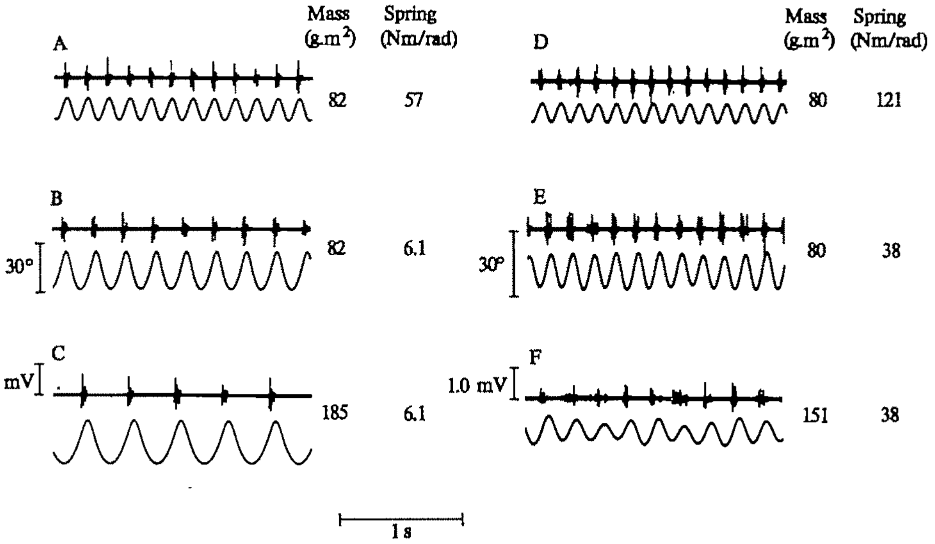


FIG. 8. Records of spontaneous clonus. Each sample of record shows joint movement (dorsiflexion upward), and soleus EMG. The mass (moment of inertia in g.m^2) and the spring stiffness (Nm/rad) are shown beside each record. A to C are from the same spastic subject as fig. 5D. The spring applied just sufficient dorsiflexing force to bring the mean position of the foot up to an angle of 90 deg with the anterior border of the tibia. D to F are from a normal subject. He was instructed to keep his foot at the same 90 deg angle. A meter display of position helped him to do so, but the spring was adjusted so that this required a mean plantarflexing force of 4 Nm. Note that calibrations for A to C differ from those for D to F. Time scale is the same for all records.

Spontaneous Clonus

Spastic subjects. Many of our spastic subjects exhibited spontaneous clonus when a small dorsiflexing force was applied to the sole of the foot. In 8 of these we examined the effects on the joint of different spring-mass loads. Fig. 7 is a diagram of the experimental arrangement which enabled us to change the spring or the mass that was attached to the foot, without altering the mean dorsiflexing force.

Figs. 8A to C are 3 samples of clonus recorded from the same spastic subject as fig. 5D. Different spring-mass combinations were used for the 3 records, and there were corresponding changes in the clonus frequency. With a large mass and a compliant spring (fig. 8C), the movement had a frequency of 2.6 Hz, but when the mass was reduced (fig. 8B), its frequency increased to 4 Hz, and with a stiffer spring (fig. 8A) it increased further to 5.7 Hz.

A further and even clearer demonstration of the effects of load was obtained when records from longer periods of the same clonus were subjected to spectral analysis. Fig. 9 shows the frequency and amplitude of the clonus with 7 different load combinations. As the moment of inertia was increased (records C to F), the frequency of movement progressively decreased, but when the inertia was further increased (G), the amplitude of the movement decreased abruptly and such movement as remained was less regular and at a somewhat higher frequency. When the moment of inertia was held constant, and the spring stiffness was increased (records C to A), the frequency of the clonus increased up to 5.7 Hz.

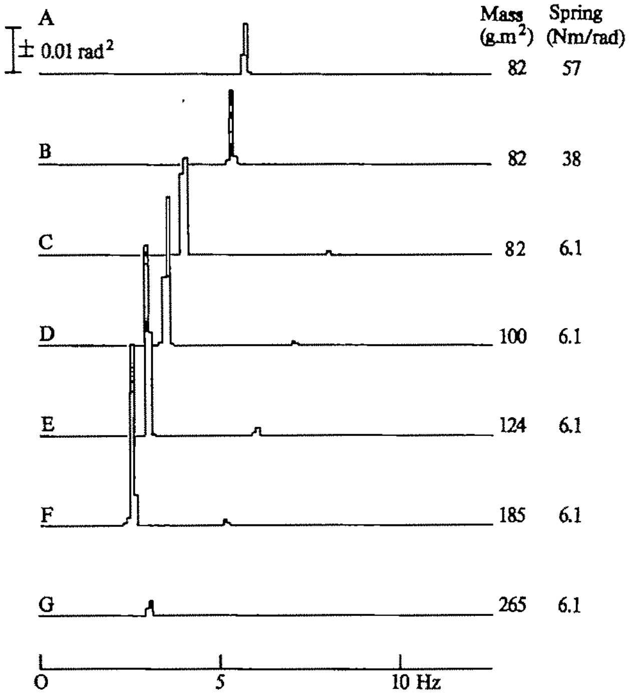


FIG. 9. The effect of load on clonus. Position records were subjected to spectral analysis (*see* Brown *et al.*, 1982*d*), using a sampling rate of 25/s, bin widths of 0.1 Hz, and 10 s or more of each record. Each record was obtained with a different spring-mass combination attached to the foot (indicated on the right). A, C and F were from the same records as fig. 8A to C. These are power spectra in which the vertical scale has the dimension Amplitude², which exaggerates the differences between the records.

In this subject the frequency of clonus could be 'moved' between 2.5 and 5.7 Hz by changing the mechanical load. It will be noted that during sinusoidal movements of the same limb (fig. 5D) it was in this same frequency range that the force positively assisted the movement (the vector lay below the horizontal axis). When the load was changed even further, by the use of still larger masses or stiffer springs, the amplitude of the movement decreased abruptly, and such movement as remained was no longer a regular and forceful clonus.

Essentially similar results were obtained from the other spastic subjects. Alterations in the mechanical load changed their clonus through a range of frequencies, although this was not always the same range as in fig. 9. The frequencies at which clonus might occur could be predicted from the responses to sinusoidal driving. In fig. 5E the 3 to 4.5 Hz vectors lay below the horizontal axis, and it was at these frequencies that clonus occurred, whereas in fig. 5F the clonus occurred at 5 to 6 Hz. In each case the frequency could be 'moved' within this range by changing the mechanical load.

Normal subjects. After a prolonged period of driving, some of our normal subjects showed responses to the sinusoidal movement that were very similar to those of the spastic patients; if at the same time they exerted a voluntary flexing force, then most of them showed this type of response. There was then a range of frequencies within which the muscles were assisting the movement, and the path of the stiffness vectors passed below the horizontal axis (fig. 5B and C). These normal subjects could be expected to exhibit clonus in that frequency range, and this was usually the case. Fig. 8D to F shows spontaneous clonus in a normal subject who was exerting a small (4 Nm) mean plantarflexing force. The frequency of this clonus could also be changed by alteration of the mechanical load. In fig. 8 it changed from 4.5 to 6.4 Hz. It was, however, less consistent and less predictable than in the spastic subjects, which was hardly surprising since the normal reflex state depended always on the movement of the limb during the preceding minutes, and this inevitably changed during the course of the experiment.

DISCUSSION

The Similarity of Normal and Spastic Reflexes

When the stretch reflexes of normal and spastic limbs are compared, it is the spastic subjects who show stereotyped behaviour while the normals show a wide variety of different responses. It appears that the reflexes of a spastic limb are 'set' in a state of exaggerated excitability which is at one end of a normal range; normal subjects exhibit these same enhanced responses, but only when the reflex pathway has been 'facilitated' in an appropriate way.

The facilitation of the stretch reflex pathway that accompanies a voluntary effort is well known (Marsden *et al.*, 1972; Joyce *et al.*, 1974; Brown *et al.*, 1982*c*), but in these normal subjects facilitation of the stretch reflex also occurred without the background of continuous muscle contraction (figs. 3B and 4B); furthermore, it is a spinal reflex that was potentiated in this way (Evans *et al.*, 1983). In the present experiments, normal stretch reflexes were facilitated by subjecting limbs to prolonged sinusoidal driving, and although the results demonstrate that a large increase in reflex gain is within the repertoire of the normal nervous system, it has to be added that repeated alternating movements are an unusual and unphysiological stimulus. It is possible that under more normal conditions the nervous system can adjust the gain of the stretch reflex in useful ways and set it at levels that would be optimal for whatever task is in hand.

When stretch reflexes operate with a high gain, limbs may break into spontaneous clonus (fig. 8), and this has been observed at a number of normal joints (Robson, 1959; Joyce and Rack, 1974; Rack, 1978; Brown *et al.*, 1982*c*) as well as in spastic subjects. In everyday life, clonus of this type occasionally does occur when a large force is exerted against an 'awkward' load, and it may seriously interfere with voluntary control. In general, however, we avoid this oscillating state; presumably the ability to set the gain of the stretch reflex to high levels is reserved for periods which are so brief that the oscillatory movements have no time to build up (*see* Rack, 1981*b*).

Differences between Normal and Spastic Reflexes

Spastic subjects differed from normals in the frequency ranges within which reflex responses were concentrated into alternate cycles. The presence of short bursts of activity in alternate cycles implies that motoneurons were then discharging at only half of the frequency of the movement (or less). The frequency of the driving mechanism was then presumably higher than the 'preferred' firing frequency of those neurons at that time. Motoneurons of spastic subjects are known to discharge at lower than normal rates (Rosenfalck and Andreassen, 1980), perhaps because of a more intense and prolonged recurrent inhibition (Katz and Pierrot-Deseilligny, 1982). This difference in motoneuron behaviour could well account for the fact that the alternation of soleus activity extended down to lower frequencies in the spastic than in the normal limbs; their lower rates of discharge would make them unable to follow such high frequencies of movement. The mechanisms which may lock together the activity of a whole motoneuron pool into alternate cycles are discussed elsewhere (Evans *et al.*, 1983).

At lower frequencies, a prolonged recurrent inhibition could still affect the timing of the reflex response, even though the EMG bursts were then present and equal in all cycles. If, during each lengthening movement, the increasing muscle spindle afferent activity arrived at motoneurons when they were still somewhat inhibited after their preceding discharge, their threshold would be higher, and would only be reached later in the cycle when the afferent activity had risen to a correspondingly higher level. The reflex response to each cycle of movement would thus be retarded by the recurrent inhibition, and this retardation would occur in a frequency range determined by the duration of the inhibition. If this were more prolonged in spastic subjects (Katz and Pierrot-Deseilligny, 1982), it could account for the fact that responses to some frequencies of movement (6 to 7 Hz) were appreciably later than in the normals.

The Nature of Ankle Clonus

Vector displays of the resistance to sinusoidal movement give a useful insight into the stability of the reflex mechanism, and the likelihood of spontaneous oscillations. Whenever the force vector passes below the horizontal axis, as it did at some frequencies in figs. 5B to F, the limb was doing work on the driving machine, and thus tending to maintain its own movement (Brown *et al.*, 1982*d*). If the path of a vector should pass through or surround the zero point, then it might be expected that the joint would oscillate spontaneously if it were free to do so (Rack, 1981*a*).

None of the vector paths of fig. 5 actually surround the origin, but these figures represent only the forces at the joint, and do not include forces required to move the mass of the foot, or any other additional load. It is, however, possible to calculate the forces required to move a mass or spring, and thus to show how either of them would modify the path of a vector. The results of one such calculation are illustrated in fig. 10, where the data of fig. 5D (shown here as a broken line) have been replotted (continuous line) as they would have been if a particular mass and spring had been attached to the foot. The path of the vector now passes beneath and around the origin, and a spontaneous oscillation of reflex origin would be expected if the foot were free to move while loaded in this way. The spring and mass that were chosen for this calculation were the same combination that in figs. 8B and 9 led to a

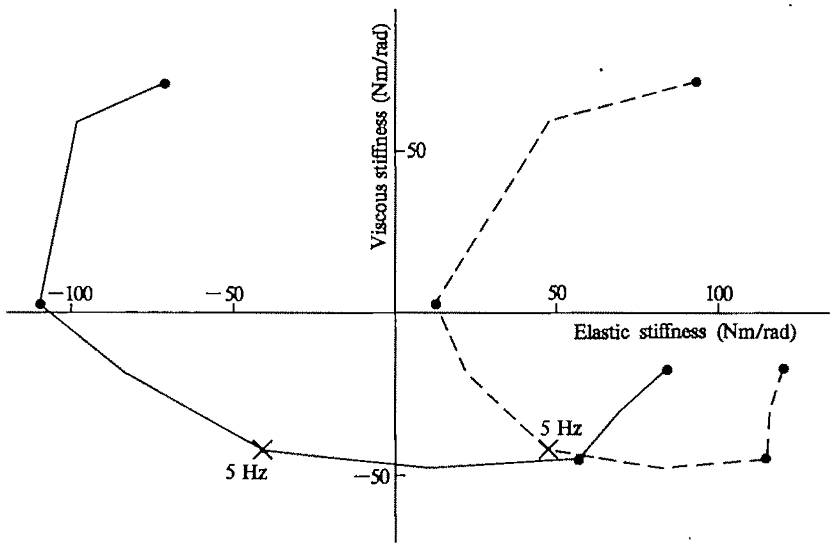


FIG. 10. The effect of a spring-mass load on the responses to sinusoidal driving. The stiffness vectors of fig. 5D have been replotted (broken lines). The continuous line shows the path that the vectors would have taken if a mass (moment of inertia = 82 g.m^2) and a spring (stiffness equivalent to 6.1 Nm/rad) had been attached to the foot.

spontaneous clonus at about 4 Hz. The path of the vector was undoubtedly determined by the combination of the stretch reflex and the mechanical load, and the fact that spontaneous clonus did indeed occur with this load provides convincing evidence of the involvement of the stretch reflex in clonus.

In the present experiments the addition of inertia or the attachment of springs changed the clonus frequencies of both normal and spastic subjects, and changed them through ranges in which the limbs had been shown to do work on the driving machine. This result confirms the fact that although clonus arose from the operation of a highly active stretch reflex, its precise frequency depended on the mechanical load at the joint. Similar results were found at the elbow joint (Robson, 1959; Joyce and Rack, 1974) and the interphalangeal joint of the thumb (Brown *et al.*, 1982*d*).

In a linear system the responses to sinusoidal driving would enable the frequency and course of an oscillation to be predicted quite precisely. The mechanisms which control human limbs are, however, far from linear, so that the amplitude of clonus cannot be predicted from the responses to a single amplitude of movement; nor is the frequency of a large clonic movement necessarily related to the load in exactly the way that might be expected from the responses to smaller driven movements.

The results reported here appear to be in conflict with those of some other workers who were unable to change the frequency of clonus by the addition of mass (Walsh, 1976; Dimitrijevic *et al.*, 1978, 1980). In agreement with Dimitrijevic *et al.* we conclude that clonus is the self-sustaining oscillation of a stretch reflex pathway; however, the changes in frequency that result from the use of adequately stiff springs or large masses (figs. 8 and 9) strengthen our conclusion (*see* Rack *et al.*, 1983) that central mechanisms do not have the dominant effect on the frequency of clonus which those authors have suggested.

ACKNOWLEDGEMENTS

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NOTICES OF RECENT PUBLICATIONS

Schmerz. By Wolfgang Larbig. 1982. Pp. 376. Stuttgart: Verlag W. Kohlhammer. Price DM 98.00.

Professor Larbig's book is different from most books on pain as a large part is concerned with trance states, states of being possessed and states of religious ecstasy in relation to not feeling pain. These unusual features of the book include experiments on Greek fire-walkers and on a fakir. Fire-walking has been practised for more than 2000 years in south-east Europe and the Middle East, where it is associated with religion. It is also performed in some Polynesian islands, India, Mauritius, among the Bushmen of South Africa, in Japan, Siberia, and among the Cheyenne Indians of North America. Larbig without doubt has a great deal of knowledge of this subject and these sections of his book are based on his investigations of Greek fire-walkers. Having found that those taking part in the ceremony of walking on red-hot coals have no signs of burns on their feet, Larbig and his colleagues examined in the laboratory the physical aspects of fire-walking. Under the same conditions as in Greece, none of the four German volunteers got their feet burned and none of them had pain. The reasons for the lack of burning and pain were found to be that thick skin with a thick horny layer is a bad conductor of heat (which was confirmed on a corpse); that peripheral sweating is probably increased; that the actual fire dance consists of leaving the feet in contact with the glowing coals for 0.20 to 0.25 s and keeping them away for 0.35 to 0.40 s; that immediately after performing these steps, the dancer has to walk on the relatively cool earth so that his feet lose heat rapidly. Larbig and colleagues also observed that the pressure of the feet on the glowing coal puts out the glow; for this to occur, the coals have to have only a superficial depth of red-hot glow. As would be expected with physical factors that need to be exact, it is not always successful; burns do occur. It is common for small points of burns to be found, where the ash became detached from the coal and stuck to the sole. Their conclusion about pain and fire-walking is that there is no pain to overcome, as the physical factors are insufficient to cause adequate degrees of burning. Just before stepping on the glowing coal and during the fire-dance, many of the participants had theta activity in the EEG. Its amplitude increased while the subjects were actually on the red-hot coal.

Larbig and his colleagues then investigated a fakir who earned his living by giving evening performances in which he passed daggers subcutaneously through his abdominal wall and neck and through his tongue. He had occasionally allowed himself to be crucified, remaining on the cross for several hours, coming to no harm, unlike another well-known case. He had also been buried alive for one or two days, had reposed on a bed of nails, and sat in a tub of flaming benzene, and had had dental treatment and an appendicectomy without anaesthesia. During these escapades, he had put himself into a trance state.

This fakir had suffered from much ill health and pain during childhood. He had then discovered that if he gave way to the pain and moved about and shouted, the pain became worse; if he lay quietly and thought of pleasant or neutral things, the pain was less. He then undertook a systematic pain-control training. He tried experiments with his mother's knitting needles, putting them through the skin of his forearms, while attempting not to feel pain. A part of this training was that he fixed his vision on a hole in the wall thus inducing a trance-like state.

When he was investigated, his neurological state was normal; he had no form of congenital analgesia. Indeed, when he was not in his induced trance state, he appeared to have a low threshold for pain, not only complaining of pain on venepuncture and lumbar puncture but also from the sphygmomanometer cuff on his arm. The investigations undertaken were EEG, electroretinography, skin conductance, many biochemical examinations including beta-endorphin and met-enkephalin estimation in the CSF. Except for the latter examinations, which were carried out afterwards, the examinations were performed while the fakir passed daggers through the skin of his thigh, abdominal wall, neck and tongue. He manifested no evidence of pain and there was no bleeding. The main findings were increased skin conductance, an increase in plasma adrenalin and noradrenalin with a later reduction of plasma dopamine to nil, and slow theta waves in the EEG over the parietal areas.

Larbig found that an increased parietal theta activity of high amplitude was common to the fakir, some fire-walkers and two volunteers. The occurrence of these waves in the EEG was contemporaneous with the trance-like state, although Larbig considered that its occurrence in some fire-walkers was an epiphenomenon, for they had no pain to reduce or inhibit. He also emphasizes that in the case of the fakir, inhibition of pain applied only to the self-inflicted painful stimuli and was not generalized to other sources of pain, as for example in having his blood pressure taken, which he considered to be painful.

Larbig reports investigations carried out on Zen Buddhist monks in Japan who have been training for twenty to forty years. They also have bursts of theta activity during the final stage of meditation. He discusses in detail the significance of theta activity. An increase in theta activity occurs also in other cases of changes in consciousness, with 'narrowing of the field of attention'. Larbig asks the question whether the change in state of consciousness is associated with corticofugal inhibitory effects on the nociceptive input.

This is a book that will interest neurologists and physiologists; but it should have been edited, as it is often repetitive. It is unnecessarily long, for it includes pages on telemetering in general, quotations given in full instead of merely giving the reference, pages on measuring pain, all of which is well-known, and chapters on American psychology, most of which are scarcely relevant. The long section on hypnosis with many references is a good account and will be useful for anyone who needs to look up this subject. The book is up-to-date on behaviour therapy and American cognitive strategies to combat pain. Altogether this is an exceptional book and contains a great deal of material that is not easily found elsewhere.

P. W. Nathan

Skeletal Muscle Pathology. Edited by F. L. Mastaglia and Sir John Walton. 1982. Pp. 648. Edinburgh: Churchill Livingstone. No price stated.

Pathologie der Muskulatur. By J. M. Schröder. 1982. Pp. 813. Berlin: Springer-Verlag. No price stated.

Muscle diseases, in their presentation, span many medical disciplines. In the English-speaking literature, the first comprehensive account of the different aspects of myopathology was *Diseases of Muscle: a Study in Pathology* by Adams, Denny-Brown and Pearson. This was first published in 1953. It set the stage for a rapid expansion in the subject made possible by the introduction of new histochemical techniques, electron microscopy and biochemical studies. The tradition was continued by *Disorders of Voluntary Muscle*, edited by John Walton and first published in 1964. Now in its fourth edition it is still the standard reference work in the subject although it is beginning to show signs of age and a lack of freshness in some of its contributions. *Skeletal Muscle Pathology*, a new multiauthor work edited by Frank Mastaglia and Sir John Walton is, in a sense, a companion volume. It aims to produce a comprehensive account of muscle pathology, dealing with the histological, histochemical and ultrastructural changes and with the fundamental biochemistry and immunology of neuromuscular disorders. It is a conspicuous success. The contributors have been well chosen and have produced authoritative, readable, and beautifully illustrated chapters. Despite its size, with the attendant and unavoidable delays in publication, it is remarkably up to date.

John Walton worked in Boston with Raymond Adams. So did Michael Schröder, author of the second book on myopathology reviewed here, emphasizing the seminal influence that Raymond Adams had on the subject. *Pathologie der Muskulatur*, in contrast to the first book, is a single-author work, although nearly 200 pages longer. It is again remarkably comprehensive but its appeal will inevitably be restricted as it is only available in German. It is extensively referenced and will prove to be a valuable asset in this respect.

P. K. THOMAS

The Genetics of Neurological Disorders. By Michael Baraitser. 1982. Pp. 516. Oxford: Oxford Medical Publications. Price £35.00.

Neurology, as a discipline, attracts its fair share of genetically determined conditions. The standard source of reference for practising neurologists has been the late R. T. C. Pratt's *The Genetics of Neurological Disorders*, published in 1967, but now inevitably out of date because of the substantial advances in genetics since its appearance. In the Preface to Michael Baraitser's book with the same title, the author points out that it is a basic human need to know what went wrong, whether it will happen again, and whether it can be prevented, even if no active treatment is available. This is the pointer to one of the particular advantages of Baraitser's book. Not only is it comprehensive but, in addition to providing clinical descriptions, necessary for the recognition of disorders, and giving accounts of inheritance patterns, it is remarkably helpful in providing advice on common (and rare) clinical problems relating to recurrence risks and the likelihood of transmission. This is particularly important where the mode of transmission is uncertain and empirical risks have to be provided.

One of the merits of Pratt's book was the vast reference list that was included. Readers of its successor will not be disappointed on this count, although the discussion of the literature is not always highly critical.

This is a worthy replacement for Pratt's compendious and scholarly *Genetics of Neurological Disorders*. It is a different sort of book and should be judged as such.

P. K. THOMAS

Genetics in Neurology. By V. Ionasescu and H. Zellweger. 1983. Pp. 505. New York: Raven Press. Price $73.00.

This 'volume of combined clinical neurogenetics and genetic neuropathophysiology' is introduced by a useful chapter on basic genetic principles. The following 17 chapters systematically cover the clinical, biochemical, pathological and genetic aspects of many monogenic and polygenic neurological disorders. At least one third of the volume is devoted to what can broadly be called inborn errors of metabolism.

On the supposition that most potential purchasers of this book might turn to it for practical advice from time to time, I have sought within it the answers to a number of clinical questions which have arisen in the last few months. The authors state in their preface that 'the main goal of this monograph is to emphasize the genetic aspects of neurological disorders'. I was therefore rather surprised to find no mention of multiple sclerosis in either the index or the text. The same applied to Leber's optic atrophy. There was little assistance in giving genetic advice to the patient with scapuloperoneal myopathy who had no similarly affected relatives. I was unable to establish the likelihood of X-linked inheritance in a single male case of early onset cerebellar ataxia with associated pyramidal signs. In relation to the vexing question of anticonvulsant medication in pregnancy, it cannot have escaped the attention of most neurologists that 'it is certainly advantageous . . . for mothers to take no anticonvulsive medication. However, grand mal seizures should be prevented by all means'.

This book cannot be wholeheartedly recommended, particularly to adult neurologists. It is well referenced and up to date, but there are few illustrative photographs and the English is obscure at times. It is also relatively expensive.

A. E. HARDING

Companion to Psychiatric Studies. Edited by R. E. Kendell and A. K. Zealley. Third Edition. 1983. Pp. 719. Edinburgh: Churchill Livingstone. Price £30.00.

This is the third edition of a multi-authored psychiatric textbook which was initially introduced specifically for candidates taking the examination for membership of the Royal College of Psychiatrists. That first companion, published in two volumes in 1973 has, in the course of new editions, been brought together into one manageable book, and it is no longer specifically tailored to an examination syllabus. In this edition, many of the chapters are new and others have been extensively revised, although it still retains its Edinburgh bias in the sense that, with few exceptions, the majority of its authors are from Scotland and many from that particular city.

The neurologist looking for an up-to-date textbook of psychiatry, either to recommend to his students, or wishing to have a brief text for himself, would probably turn to the chapters which are more related to organic brain syndromes to get a flavour of the overall quality of the book. He would find that the majority of references were ten years old, and that if he examined a specific sub section, such as that on epilepsy, no reference after 1973 was given, ignoring almost a decade of research in the fascinating and active field of the links between psychiatry and epilepsy. He would also note in that section some unconventional definitions, and no reference to the now widely used international classification. In searching for hints regarding treatment of difficult neuropsychiatric problems he would again be disappointed, as such practical advice does not emerge.

Perhaps discouraged, the potential purchaser would then flip through the rest of this substantial volume. Schizophrenia is an important field where many studies have outlined the underlying organic substrate, and new research in this field has highlighted the importance of full investigation, including CT scanning for patients. However, little mention is made of the now extensive studies on CT scans in schizophrenic patients and the growing interest in Crow's type 1 and type 2 schizophrenia has been overlooked.

With some disappointment therefore, acknowledging the book has over 700 pages and costs £30, the conclusion would probably be that this was not the most appropriate textbook of psychiatry for the neurologist to purchase. In the opinion of this reviewer, there is still room for a compact psychiatric textbook, with a low price, which would emphasize the important aspects of psychiatry for neurologists and complement the relative profusion of books which have emerged recently which attempt to present neurology to psychiatrists.

MICHAEL R. TRIMBLE

Progress in Neuropathology. Volume 5. Edited by Harry M. Zimmerman. 1982. Pp. 355. New York: Raven Press. Price $73.16.

It is difficult to appreciate that we are already at Volume 5 of this excellent series, and that it is twelve years since the first volume was published. This can only be seen as a tribute to the unfailing energy and foresight of Harry Zimmerman, recently elected to Honorary Membership of the International Society of Neuropathology—the highest honour that neuropathologists can pay to any of their colleagues.

There are 13 chapters covering a wide range of topics. Inevitably they are of mixed quality and interest but the editor's aim has again been achieved, namely 'to publish original, innovative and stimulating studies that may point new directions in the field of neuropathology'. This is well exemplified by the first chapter by Ingrid Allen on multiple sclerosis. She reviews the place that hydrolytic enzymes may play in the causation of the disease but has to conclude, as is so often the case in studies on multiple sclerosis, that further study is necessary. But in which direction? She also reminds us that there are diffuse abnormalities in white matter in this disease.

The next two chapters deal with immunocytochemistry—Eng and DeArmond on glial fibrillary acidic protein, and Pearson in one of the longest chapters in the book on neurotransmitter immunocytochemistry. Both subjects are fully and competently reviewed and illustrated. To someone, like this reviewer, not well acquainted with this field, Pearson's chapter brings home to one how easy it can be—with proper controls—to distinguish different axonal populations in areas that on conventional microscopy are a 'bewildering labyrinth of morphologically repetitive components'. Then Hirano, a man never short of new ideas or concepts, reviews the periaxonal space and its reaction to some pathological processes. As one would expect, his contribution is fully and impeccably illustrated. He concludes that this is a rather special space and that changes in the interface between the myelin-forming cell and the axon might be the source of important clues regarding the pathological processes leading to demyelination and/or axonal alterations. Rammohan and his colleagues tackle the important question in experimental models of the persistence of measles virus in the nervous system, and provide a comprehensive and interesting review of the current situation. One can only hope that further experimental work in this field will help to shed some light on subacute sclerosing panencephalitis and perhaps multiple sclerosis.

The next chapter is by Wisniéwski and his group on paired helical filaments and amyloid fibres, and reviews in depth the possible causes of the development of amyloid in dementia of Alzheimer type. I was interested to note that there was no attempt to equate conventional senile plaques of Alzheimer type to the amyloid-containing plaques sometimes observed in the spongiform encephalopathies. The two types of plaque are so different when examined by conventional microscopy that I sometimes feel that too great an effort has been made in recent years to persuade us that they have close similarities.

The next chapter is on the entity of neuromicroangiopathy in encephalomyocarditis-virus-induced diabetic mice by Mukai and colleagues. This is an interesting and well illustrated contribution and although some readers might not be aware of the condition, clearly any studies that shed some light on diabetic microangiopathy are to be welcomed.

The next two chapters are devoted to treatment—enzyme replacement treatment of Tay-Sachs disease brain cells *in vitro* (Adachi *et al.*) and natural therapeutic agents (Vogel). The first of these tells us that at the cellular level Tay-Sachs disease cells can be favourably modified by the intracellular incorporation of a purified therapeutic enzyme preparation, and suggests that if the problems involved with *in vivo* delivery could be overcome, some degree of clinical improvement might be achieved in affected individuals. Perhaps too early for enthusiasm but an interesting observation. Vogel's short chapter is a delight to read.

There then follows an account of Creutzfeldt-Jacob disease in man and laboratory animals (Tateishi *et al.*) emphasizing some rather atypical features, and this is followed by a perhaps rather mundane account of the ultrastructure of pituitary adenomas (Roy). Llena's chapter on paraganglioma is particularly welcome at this time and, as he states, is a short selective review of the paraganglion system and paragangliomas, and an analysis of the group of paragangliomas reported to arise primarily along the cerebrospinal axis. This is really an excellent concise account of the situation. Finally, there is an authoritative chapter by Oehmichen on inflammatory cells in the central nervous system.

In some ways this is not an easy book to review since very few individuals could possibly comment authoritatively on the wide range of topics covered. On the other hand, such a beautifully produced, well illustrated and well referenced book like this needs hardly to be reviewed since it must be available to and read by, at least selectively, all with an active interest in the neurosciences.

J. HUME ADAMS

Immunology of Nervous System Infections. Progress in Brain Research. Volume 59. Edited by P. O. Behan, V. ter Meulen and F. Clifford Rose. 1983. Pp. 394. Amsterdam: Elsevier. Price Dfl. 245.00.

This book is made up of 38 different contributions from scientists and physicians from all over the world who, because of their expertise, took part in the proceedings of the Noble Bodman Symposium on 'Immunological Aspects of Acute and Chronic Nervous Disorders', held in London on November 12 and 13, 1981 at Lettsom House (Medical Society of London).

Considering the great difficulty in editing works of this nature, it has been brought out soon enough after the meeting for the work still to be up to date in a rapidly advancing field of knowledge. Much of the book is devoted to the role of viruses in the causation of neurological disease. The subjects considered include: how viruses such as herpes remain latent and may be reactivated, the role of interferon in acute and chronic viral infections, the modulation of viral antigens, and how this may be a mechanism for viral persistence. General immunosuppressive effects of virus infection are elaborated and explained, and the effect of viruses and immunodeficiency diseases is examined in some detail. There are several contributions on SSPE; the immunological factors and antigenic changes which may occur in measles virus which contribute to the disease process, and the therapeutic attempts to treat the disease, are explored. The use of animal models to try to understand better the pathogenesis of CNS demyelination takes up several contributions. These include Corona virus—JHM, and Semliki Forest virus demyelination in mice, in both of which immunological mechanisms, particularly lymphocytes, appear to play an important part in pathogenesis. It is also stressed that the strain of virus used for these infections, combined with factors such as age, immune status, and genetic background, are very important in the development of the lesion and the demyelination. In the vaccinia and canine distemper demyelination model seen in dogs, some interesting work is presented with reference to possible virus-induced autoimmunity to the myelin oligodendrocytic compartment. There are several contributions on the role of both humoral and cellular immunity in the production of experimental allergic encephalomyelitis, one explaining how the possible interaction of cellular and humoral immune mechanisms may be important in the development of the disease process.

A chapter on the therapeutic value of interferon in many different virus diseases is of considerable interest.

One group has used an age-dependent motor neuron disease in C58 mice as a model to try to explain how ageing, viral infection, genetic factors and immune deficiency act together to predispose mice to paralytic disease. Their findings are discussed in relation to the basic mechanisms that may be important in the pathogenesis of the age-dependent neurological diseases of man of suspected viral aetiology.

Only one chapter is on spongiform encephalopathy agents. This refers to scrapie and to the mechanisms involved in the formation of amyloid plaques, and how they may be of some interest in relation to Alzheimer's disease in man. There are also several papers on immune responses in multiple sclerosis in relation to cell-mediated immunity during the disease process. One of interest concerns the humoral and cellular immune responses in MS serum and CSF to staphylococcal lipoteichoic acid. The biological activity of this substance appears to be dependent on its membrane binding properties *via* the lipid (glycolipid) part of the molecule. This substance was able to produce encephalitis on repeated inoculation into rabbits. The role of glycolipids as possible immunogenic mediators in the development of MS is becoming increasingly interesting.

This is a good book, well presented, with stimulating experimental and hypothetical contributions which are of considerable interest both to clinicians and scientists. The quality of the plates—graphs, and light and electron micrographs—are excellent. The book shows how far immunological techniques have advanced for studying the immunopathogenesis of disease. It is quite clear that the theme running through the book is that the strain of infecting antigen, the immunological status of the host, the genetic make-up, and the age when the infection is acquired, are, in combination, all important factors. In many of the papers it is the T-lymphocyte in its various roles which seems to stand out as the cell whose activity is in greatest need of being understood at present. The problems of virus-induced autoimmunity still remains an enigma. Some of the papers put forward mechanisms which may be involved. The book should greatly stimulate ideas for further research directed at solving the mechanisms of pathogenesis of these fascinating diseases and in so doing, may perhaps lead to the development of rational modes of prevention and therapy.

H. E. Webb

An Introduction to Neurophysiology. By J. F. Stein. 1982. Pp. 386. Oxford: Blackwell. Price £12.00.

The intent of the author of this introductory textbook is admirable, which is to 'convey the fascination and excitement of neurophysiology'. To do that, and in order to cover the whole of neurophysiology, he has been selective in his choice of experimental results to be described and has included 'far more speculation than one would normally expect to find in a textbook'.

In a great part he has been successful and the book generally reads very well: for each system that he describes we are constantly brought back to the physiological role which that system subserves. Where the book falls down, for me, is in the detail. I looked at the areas I know well. First, the nervous control of respiration is quite inadequately dealt with and is described under the autonomic nervous system, as if the effectors were part of that system, which of course they are not. The one illustration for this section is described in the text as representing a disproved theory, but nevertheless, being the only illustration, is likely to be remembered by a student reader. Secondly, in the spinal cord section there are many minor mistakes, such as putting the Ia inhibitory interneurons in lamina IX instead of lamina VII or the misuse of the term $A\beta$ to refer to the β innervation of muscle spindles. Here also there are some slightly unfortunate generalizations, for example that the ideas of spatial and temporal summation are only appropriate to complex reflexes (such as the flexion reflex) or that 'the general concept of servo-action is the one which many people find the most useful to characterize spinal cord operations'. This latter statement is denied as being the author's view in the next few sentences. But is it really the view of any modern, or indeed former authority? What about spinal locomotor half-centres for instances?

There are similar errors and loose descriptions elsewhere such as 'Receptors in the periphery (skin, eyes, ears, etc.) connect with sensory nerve fibres' (p. 2), 'synaptic noise' wrongly used (fig. 4.3) or diagram of a Voigt element (fig. 3.11) which must confuse rather than help a naïve reader.

Perhaps one should not cavil at such relatively minor lapses when the author's intent to give an overview is mostly so successful, with a very wide field covered in only 350 pages. The introductory sections on electrical properties and synaptic transmission are concise and, on the whole, well explained. The integration of evidence from neuroanatomical, neurophysiological and neurological sources in the sections on the higher functions of the nervous system is smoothy achieved and one gets a good feeling for why one does or does not know how to explain a particular phenomenon, for instance, why there are no simple analogies in the investigations of motor systems to the strategies that have been so successful for investigating sensory systems, at least at the lower levels.

The greatest value of this book will be to give a general feel for the whole subject of neurophysiology and perhaps therefore arouse an interest in it for those who are new to the field. There are few references in the text but a quite useful bibliography organized by chapters, a very condensed historical epilogue, and an apparently comprehensive index.

P. A. Kirkwood

Abnormal Nerves and Muscles as Impulse Generators. Edited by W. J. Culp and José Ochoa. 1982. Pp. 750. Oxford University Press. Price £40.00.

Over the last two decades the boundaries between the traditional subjects of anatomy, physiology and biochemistry have been obscured by the growth of neuroscience, an interdisciplinary subject reflecting widespread interest, from many points of view, in the nervous systems of different species, their development and the nature of the mechanisms they employ. In relation to clinical neurology this subject is characterized by a much greater emphasis on structure and function at the cellular, membrane and molecular level than was the case in previous years, when studies of the integrative action of the nervous system held sway but when the search for animal models of human neurological disease was often hampered by major interspecies differences in the organization of nervous systems. One important consequence is that questions posed at the cellular, membrane or molecular level are more easily generalized and better suited to allow a meaningful dialogue between basic and clinical scientists. Such a dialogue led William Culp, a biochemist and José Ochoa, a clinical neurologist to organize an important meeting in Dartmouth, New Hampshire, the first of its kind on the topic 'Abnormal Nerves and Muscles as generators of impulses'. The present book represents the expanded and updated papers contributed by the large number of distinguished research workers who were present.

The aim of the meeting was to define a set of 'positive' clinical phenomena, that is, 'irritative' manifestations of neurological disease such as paraesthesiae, neuralgias and involuntary movements, and to discuss their mechanism in the light of current knowledge of the structure, biochemistry and electrophysiology of nerve and muscle. The book is comprised of 35 chapters and its scope is well represented by the titles of its 6 principal sections, 'structure and function of excitable membranes'; 'excitation impulse initiation and conduction'; 'spontaneous impulse generation in neurons'; 'spontaneous impulse generation in the human motor unit'; 'spontaneous discharges in the sensory unit'; 'muscle fibres as impulse generators'. A preface by J. Diamond and the editors sets the scene with admirable clarity to provide a standard that is maintained throughout the book. The contents of the chapters range from the relatively recently introduced method of 'patch clamping' for the study of 'gating' and permeability changes associated with single ion channels in membranes, to a consideration of the physiological consequences in the spinal cord of damage to peripheral nerves. Between these extremes are chapters dealing, on the one hand, with virtually every aspect of ictal phenomena encountered in clinical neurology and on the other, with corresponding or relevant fundamental studies such as the basis of ectopic impulse generation in central and peripheral nerve fibres or the electrogenesis of fibrillation potentials. Thus basic and clinical scientists alike cannot fail to find interest and new knowledge within these pages. In short, this book well exemplifies how the interdisciplinary approach of neuroscience provides a common ground where basic and clinical scientists can share their different kinds of knowledge and experience.

T. A. SEARS

Electrodiagnosis in Diseases of Nerve and Muscle. Principles and Practice. By Jun Kimura. 1983. Pp. 672. Philadelphia: F. A. Davis. Price $81.25.

Dr Kimura's 672-page textbook includes a glossary of terms used in clinical electromyography and is written in an easily readable style with many instructive illustrations. The author intended to provide a description of electrodiagnostic procedures that would be used by clinicians as an extension of the neurological examination. He has fulfilled this aim, producing a book that encompasses the entire field of electrodiagnosis in diseases of nerve and muscle.

A short introductory chapter describes the anatomy of peripheral nerves and the muscles that they innervate, with useful schematic diagrams. This is followed by a chapter on those electrical properties of nerve and muscle that are essential for the understanding and interpretation of electrophysiological findings. Another chapter deals with electrodes and recording equipment including an explanation of artefacts arising from electrodes, amplifiers, and power supply and how to avoid them. A more detailed description of fundamentals of electronics and instrumentation is available in an appendix written by two electrical engineers (P. J. Seaba and D. D. Walker).

The second part of the book is devoted to nerve conduction studies, exploring the anatomy and physiology of peripheral nerves, principles of nerve conduction determinations, assessment of individual nerves and reviewing facts, and fallacies and fancies of nerve stimulation techniques. The emphasis is on surface stimulation and recording.

Assessment of neuromuscular transmission constitutes the third section, starting with a review of anatomy and physiology of the neuromuscular junction, followed by chapters on repetitive stimulation, activation procedures and less common methods such as microelectrode recordings, tonography, impedance audiometry and electronystagmography.

The properties of the motor unit are described in terms of anatomy, histochemistry and physiology, including voluntary evoked muscle activity and types of spontaneous discharges. Different approaches to quantitative and automated analysis of the motor unit potential are mentioned. Kimura believes that an experienced electromyographer can confidently rely on observation of oscilloscope displays and audio characteristics to evaluate motor unit characteristics; not everyone would agree. The chapter on single fibre EMG (SFEMG) includes information about recording equipment as well as practical applications. Kimura regards measurement of fibre density and the variability of the interval between potentials of two or more single muscle fibres of the same motor unit ('jitter') as the most useful supplement to conventional EMG. Moreover, SFEMG is now probably the most sensitive electrodiagnostic test for the diagnosis of myasthenia gravis.

Part 5 covers the blink reflex, F wave, H reflex and somatosensory evoked potentials. This is the special interest of the author, a field to which he has contributed a great deal with respect to the establishment of normal values, and the standardization and interpretation of collected data in different central and peripheral disorders. Investigators interested in these techniques can consult this section confidently for a thorough description of methods, clinical applications and limitations.

The last two sections (parts 6 and 7) summarize signs and symptoms of different disorders of the spinal cord and peripheral nervous system as well as of diseases of the neuromuscular junction, myopathies, and abnormal muscle activity, and their electrophysiological correlates. It repeats to some degree details given in other parts of the book.

Two appendices close the book. One is a historical review on the early development of electrophysiology, classical electrodiagnosis, EMG and nerve stimulation techniques, and recent developments. The other appendix covers electronics and instrumentation.

The author is to be congratulated on this immense work, which for the newcomer interested in EMG and related electrodiagnostic tests should be the book of first choice, comprehensive and up to date as it is, with numerous references after each chapter to document statements made throughout the text.

W. TROJABORG

Electroencephalography. Basic Principles, Clinical Applications and Related Fields. Edited by Ernst Niedermeyer and Fernando Lopes da Silva. 1983. Pp. 752. Munich and Baltimore: Urban and Schwarzenberg. London: Pitman. Price £58.00.

This book is described by its principal authors as a 'large one-volume textbook' which is intended to fill the gap between the smaller introductory texts and the huge multivolume handbook. In part it succeeds in this difficult aim, and its 752 pages will surely become a standard reference work for Departments of Clinical Neurophysiology, although the price of £58 in the UK will be beyond the means of most students and indeed of many practitioners in the field.

On page 86 at the end of the chapter entitled 'The normal EEG of the waking adult', Niedermeyer observes: 'This shows clearly where the limitations of an EEG textbook lie. There is simply no firm rule concerning the manner in which the record reader's eyes and brain have to operate in this process.... There is an element of science and an element of art in a good EEG interpretation; it is the latter which defies standardisation.'

Fifteen of the 44 chapters, which together comprise more than one-third of the text, are by Niedermeyer himself and form the core of the volume. Written with enthusiasm that at times verges on the poetic, by a practitioner with a lifetime of experience and encyclopaedic knowledge, they are a 'must' for anyone interested in electroencephalography today. Not all the contributors reach these standards, but the chapters on 'Nonspecific abnormal EEG patterns' by Frank W. Sharbrough, on the very difficult subject of 'Neonatal electroencephalography' by Cesare T. Lombroso, and the chapter on 'Polygraphic recordings of sleep and sleep disorders' by Roger Broughton are worthy of special mention as well written, authoritative and most valuable reviews of their respective areas.

Particular mention must also be made of the chapter on 'Contingent negative variation' by Joseph J. Tecce and Lynn Cattanach. For those unfamiliar with this phenomenon the CNV is a 'slow potential generated in the brain that appears as a negative shift of the EEG baseline during a particular kind of reaction time task'. A stimulus (S1) serves as a preparatory signal for a second stimulus (S2) occurring after a fixed interval, usually 1-2 s later. The subject is instructed to make a motor response—e.g. press a key—to the second stimulus and the period S2-response is measured as the reaction time. The CNV was originally described by Grey Walter from the Burden Neurological Institute in the early 60s. It shows greatest promise in the study of the central nervous system actions of psychotropic drugs and may help to predict differences in response to such drugs in individual patients. The CNV response can also be used to investigate the mechanisms associated with arousal and attention. It is readily disrupted by distraction, which may be endogenous or controlled deliberately by the investigator. This phenomenon can provide a sensitive indicator of pathological deficit in these mechanisms, as in senile and presenile dementia, or in patients with anxiety states. Furthermore in normal individuals removal of the distracting stimulus is accompanied by increased amplitude of the CNV potential. This response is impaired by frontal lobe damage (e.g. in patients following prefrontal leucotomy), while conversely the duration of the potential, which normally terminates shortly after S2, has been found to be prolonged in some patients, for example, with obsessional neurosis. At an even more subtle level asymmetries in the late components of the CNV have been shown to differentiate between verbal and nonverbal stimulation in normal individuals and may prove of value in the study of dysphasia and dyslexia.

By contrast with the 'clinical' chapters the chapters on techniques and methodology are disappointing. Even Neidermeyer's own contribution—an attempt to explain the concepts underlying that central mystic phrase of EEG, the *phase reversal*, is not particularly successful. It is curious how this simple and obvious notion generates such confusion in students and reverence among neophytes. I have even seen EEG request forms where the 'Reason for referral' was given as '?phase reversal'. I think that perhaps the only solution is to proscribe the phrase altogether!

Is there something in the education or selection of the current generation of physicians that militates against the understanding of the abstract concepts of physics and electronics? The shortcomings of this book may be a reflection of this very difficulty which seems to be even more noticeable across the Atlantic than in the UK.

In the Preface the authors comment on the paradox that despite the impressive spread of EEG techniques in the fifty years since Hans Berger published his original papers, 'A certain malaise has inched its way into the hearts of thousands of electroencephalographers who have started to feel the grip of stagnation.' Niedermeyer regards this as a challenge, and in particular as a challenge to the training of electroencephalographers. This book, however, seems to reflect these difficulties as much as to offer a cure.

There is a good introduction to the basic physiology, but the two chapters on the 'Neurophysiological basis of the EEG' by Erwin-Josef Speckmann and Christian E. Elger from Munster, West Germany, and on 'Biophysical aspects of EEG and MEG generation' by Lopes da Silva with Ab Van Rotterdam, are highly technical. They would perhaps have been better at the end rather than the beginning of the text because, although useful for reference, they are not really suitable for novices at a first reading.

The chapter on the technological basis of EEG recording alternates between extremes, from the totally unhelpful—'Blocking of the amplifier due to D.C. offset voltages when switching electrode montages can easily be prevented by means of antiblocking provisions.' (This not only runs counter to practical experience, but appears in isolation with no discussion, explanation or even definition of the phenomenon of 'blocking' let alone of 'antiblocking provisions'.)—to the completely abstruse, such as the formulae developed to explain common mode rejection (3.1, 3.2, 3.3). These latter are not helped by some uncertain English, a proliferation of typographical errors and subscripts printed so small that even with a magnifying glass this reviewer cannot be certain of the difference between 'cll' and 'ell'!

The chapters on EEG recording and the EEG laboratory can be epitomized by the following quotation: 'It is critical that the patient should not sit in a way that requires one to hold the head up by muscular effort.' They would probably obtain a pass mark if submitted as essays for the ECNE qualifying examination provided that occasional solecisms were not marked too harshly. For example, 'In contrast, frequencies above the designated filter number will have progressively more than 20 or 30% attenuation so that *in all cases some higher frequencies will be attenuated down to zero amplitude* and be eliminated' [my italics].

The final chapters of this volume are also disappointing. In this case it is not that they are banal or illiterate but that masses of data are presented, often compressed to the extent of being meaningless, with minimal discussion, exposition, or guidance for the naïve reader.

Lopes da Silva, discussing the methodology and quantification of event-related potentials, correctly recognizes that '... the wide use of time averaging in practical work on EP is so overwhelming that this form of analysis will be treated extensively in the following section'. However, the subsequent discussion is almost all related to multivariate, principal component and factor analysis, none of which is, or is likely to be in the near future, in day to day practical use. Much of the rest of this chapter discusses the analysis of single trial evoked potentials but it is very difficult to disentangle what is practical from the theoretical ideals. The contrast between this section and the pragmatic approach which, as already noted forms the core of this volume, is very striking.

The subsequent chapter gives evidence of this schizoid behaviour in that the index refers to 'Clinical *evaluations* of evoked potentials' where the chapter heading says 'Clinical *applications* of evoked potentials'. The index is the more correct because this is essentially a bald account of a large number of papers, monographs and reports from which only with some difficulty can the reader deduce, for example, that the latency of the major positive component of the pattern-evoked potential is generally recognized as a useful physical sign of multiple sclerosis!

The final chapters on EEG analysis and computer-assisted EEG diagnosis are more straightforward, if only because little or no actual use has been made of any of these techniques in a clinical context. The chapters form a useful, and I think reasonably balanced, survey of the current literature. What is interesting, however, is a total lack of any references to studies in 'artificial intelligence', whether the logic-orientated Stanford school stemming from the Lederberg and Feigenbaum DENDRAL project, or the linguistic-based 'fuzzy sets' of Lofti Zadeh.

To summarize, this book mirrors the state of the art in clinical neurophysiology and reflects, rather than helps to bridge, the gap between the practising clinician and the technologist. What we need is to distill the useful, ubiquitous and robust properties from the mass of techniques and consolidate a technology. We must then explain this technology simply and train our electroencephalographers and technicians in its use so that they understand both its potential and its limitations. This book may fulfil this aim for the technology of the 60s and 70s but holds out little promise for the 80s.

H. R. TOWNSEND

Handbook of Chemical Neuroanatomy. Volume I. **Methods in Chemical Neuroanatomy.** Edited by A. Björklund and T. Hökfelt. 1983. Pp. 548. Amsterdam: Elsevier Biomedical Press. Price Dfl. 330.00.

This is the first volume in an important new Handbook series, which aims to provide a comprehensive review of the revolution which has taken place in modern neuroanatomy. The remarkable advances made in our understanding of neuronal pathways and circuits in recent years can be attributed almost entirely to the advent of powerful new techniques, and it is wholly appropriate that the first volume in this series is devoted entirely to a description of methods. These are of several types: some permit visualization of transmitter-specific neuron types; others allow tracing of neuronal connections or visualization of neuronal activity.

Historically it was the transmitter histochemistry methods which first started the 'new wave' of anatomical studies of brain transmitter systems, starting with cholinesterase staining for cholinergic pathways in the 1960s, and followed by an avalanche of studies on catecholamine and serotonin pathways using fluorescent histochemical methods in the 1970s. These were supplemented by other methods allowing monoamine localization at the ultrastructural level. In the 1980s the fashion has swung emphatically to immunohistochemical methods which allow localization of both classical amine and amino acid transmitters, and increasingly mapping of neuropeptide-containing neurones in the nervous system. Other methods exist for localizing transmitter-specific neurons, including the use of autoradiography after specific labelling with substrates that are taken up selectively by neuronal amine or amino acid uptake processes. Autoradiographic techniques have also increasingly come into use to map the distribution of transmitter and drug receptors, after binding selective radioligands to tissue sections, and autoradiography forms the basis of the deoxyglucose technique, assessing neuronal activity by increased accumulation of labelled 2-deoxyglucose in active cells. These techniques can sometimes be used simultaneously, or with retrograde and orthograde tracing techniques to prove coexistence of multiple chemical messengers in single cells, or to establish the anatomical identity of particular transmitter-specific cells. The advent of chemical neurotoxins which selectively destroy monoamine neurons (e.g. 6-hydroxydopamine) and excitotoxins (e.g. kainic acid) have also provided powerful new tools to aid the mapping of chemically identified neurons.

All these advances are ably reviewed here in a series of 13 chapters, each of substantial length. The book is amply illustrated, although I felt that the quality of the photographic reproduction was no more than adequate, and most of the figures were far too small. One hopes that these points might be improved in later volumes, particularly as this is an extremely expensive publication which relies heavily on good quality micrographs and each page seemed to contain plenty of room for increasing the size of the illustrative material. Apart from this the volume is well produced and further volumes in the series will be looked forward to. The Handbook is likely to prove an essential addition to many library shelves, and will be of interest to almost all who are connected with research in the neurosciences. The information contained here documents an important part of the advances made in our understanding of the nervous system in the last two decades. In addition the Handbook will undoubtedly serve a wider function among teachers, students and clinicians in neuroscience-related areas.

L. L. IVERSEN

Handbook of Neurochemistry. Edited by Abel Lajtha. Second Edition. New York: Plenum Press. Volume 3. **Metabolism in the Nervous System.** 1983. Pp. 698. Price $89.50. Volume 4. **Enzymes in the Nervous System.** 1983. Pp. 549. Price $72.50.

The Benzodiazepines: from Molecular Biology to Clinical Practice. Edited by Erminio Costa. 1983. Pp. 446. New York: Raven Press. Price $49.00.

The first two books represent part of the 10 volume set which comprises the Second Edition of this well established 'Handbook' series. There is no doubt that the *Handbook of Neurochemistry* will serve a useful function as a library reference work, as did the First Edition, now several years out of date. One cannot help wondering, however, if this archival approach to neurochemistry may soon outlive its usefulness. I found the present volumes contained a heavy mixture of not always related topics. Thus, in Volume 3 a first section containing 9 chapters deals with the complex lipids of nervous tissues, but the recognition of the role of lipids (gangliosides and phosphoinositides) as important cell-surface recognition molecules or as mediators of surface receptor actions receives scant attention, and is lost among a mass of other data relating to the role of lipids in myelin. Similarly, reviews of the metabolism of neurotransmitters are mixed up in an apparently disjointed way with those dealing with the metabolism of other substances in nervous tissues. Chapters on GABA, glutamate, glycine and acetylcholine are interspersed with reviews of glucose metabolism, nontransmitter amino acids, and oxidative metabolism. It might have been better to separate the material on neurotransmitters in this volume and in the next volume (which deals with enzymology in a similarly eclectic manner), from that dealing with general brain metabolism. The enzymes reviewed in Volume 4 seemed to have been chosen somewhat arbitrarily, and this was again a very mixed collection of material. The chapters on peptidases and proteinases are topical, but the question of whether 'neuropeptidases' really exist (as opposed to the metabolism of neuropeptides by nonspecific peptidases present in all tissues) is not adequately considered. In general, these volumes seemed to contain much excellent material, but their arrangement displayed little logic; one suspects that the sheer volume of detailed material may overwhelm the average reader and make it difficult to use the Handbook effectively.

Benzodiazepines: from Molecular Biology to Clinical Practice seemed likely to prove a more useful volume for those interested in this important group of psychoactive drugs. The first part of the book (8 chapters) provides an up-to-date review of the recent upsurge in basic research understanding of these compounds, since the discovery of benzodiazepine (BZ) receptors in brain membranes by radioligand binding some six years ago. The properties of these receptors, the way in which they interact with GABA receptors to enhance the synaptic effects of GABA, and the recent development of BZ antagonist drugs are well covered, together with general reviews of the experimental pharmacology and behavioural pharmacology of BZs.

The remainder of the volume comprises a series of reviews of clinical research on this group of compounds, including 8 chapters giving information on their metabolism and pharmacokinetics—an area of importance with the development of newer drugs with shortened half-lives for application as short-acting hypnotics, and the understanding that BZ half-lives are often prolonged in the elderly. The application of BZs as hypnotics and their interactions with other drugs are also covered. A final section of 9 chapters covers particular clinical applications of BZs in anxiety states, neurological disorders (including epilepsy) and their possible (but debatable) usefulness in depression and schizophrenia.

The chapters seemed to be of good quality and the volume may appeal to clinicians as a timely review of research on a widely used group of drugs. To those interested in basic research on BZs the book will hardly be adequate, and indeed this topical subject has given rise to many more extensive symposium compilations than this one in recent years.

L. L. IVERSEN

Neuroanatomical Tract-Tracing Methods. Edited by Lennart Heimer and Martine J. RoBards. 1981. Pp. 567. New York: Plenum Press. Price $49.50.

Tracing Neuronal Connections with Horseradish Peroxidase. Edited by M.-Marsel Mesulam. 1982. Pp. 251. Chichester: IBRO-Wiley. Price £11.00 (paperback).

The first of these two new and authoritative books on neuroanatomical technique aims, within the limitations of 500 or so pages of text, to present both a theoretical analysis and a practical guide for anyone who wishes to study brain structure. It surveys all aspects of experimental neurology from animal housing to modern histo-immunological techniques, while not ignoring the more traditional methods such as staining for myelin, degenerating axons and the Golgi technique. In all relevant cases the accounts take in study using the electron as well as the light microscope. The book is copiously illustrated with well chosen micrographs (many in colour) of enviably high standard, as well as flow diagrams and the like. The practical schedules are clearly set out and the result to be aimed for categorically stated in each case.

The second book is equally well produced and authoritative. The illustrations are excellent, although there are no colour plates. It devotes some 250 pages to the use of horseradish peroxidase as a neuronal tracer, whereas the more comprehensive Heimer and RoBards' volume makes over only about 150 pages to a survey of the axonal transport techniques *in toto*. The Mesulam text is therefore able to be more expansive in its discussion of the theoretical bases of the methods and to compare and contrast different techniques at greater length. Again, the potential user will find practical procedures well set out. (We have used both these books as laboratory manuals to great effect.)

The reviewer cannot see these books as rival texts, since their aims are different, the one to provide a wide basis, the other to give a penetrating analysis of one very important modern technique. Any neuroanatomical laboratory should have both.

K. E. WEBSTER

The Thalamus and Basal Telencephalon of the Cat. A Cytoarchitectonic Atlas with Stereotaxic Coordinates. By A. L. Berman and E. G. Jones. 1982. Pp. 164. University of Wisconsin Press. Price $250.00.

This is a companion volume to Alvin Berman's earlier *The Brain Stem of the Cat*, and those who know that work and expect a volume in large format (58.5 x 44.5 cm) will not be disappointed. The atlas includes those areas not covered by the earlier work, and consists of three series of figures (most of which occupy the entire area of two opposite pages) in the frontal, sagittal and horizontal planes. The frontal series of 107 plates extends from the plane just caudal to the medial geniculate bodies to the cerebral cortex of the cruciate sulcus and the caudal parts of the olfactory bulbs. The sagittal series (30 plates) extends from just beyond the median plane on one side of the brain to a plane immediately lateral to the lateral geniculate body on the other. The atlas ends with 19 plates of horizontal sections extending from the superior thalamus (nucleus lateralis dorsalis) and corpus callosum to the inferior aspect of the brainstem. All plates are derived from material cut in standard stereotaxic planes and each illustration is provided with its reference level and coordinate scales in the other two planes. When both halves of the specimen are visible, labelling is confined to one half, and no attempt has been made to draw boundary lines around any structure, be it well defined or vague.

Apart from the clarity of the illustrations afforded by the high quality printing and spacious format, a virtually unique feature of this book (as of the earlier one) is the commentary which accompanies each of the plates in the frontal series. In these notes, the authors not only comment on terminology and identification of structures by other authors, but also discuss the results of investigations of the connection patterns and functional significance of the structures they label. In this the book's progenitors are presumably the volumes by Winckler and Potter published early this century. Needless to say, the Berman and Jones book surpasses such progenitors in every way, and provides an invaluable reference work for all those actively engaged in neurological research.

K. E. WEBSTER

ERRATUM

Rehabilitation of the Neurological Patient. Edited by L. S. Illis, E. M. Sedgwick and H. J. Glanville. This book was reviewed in *Brain*, 106, p. 1022 and we regret that it was attributed to the wrong publisher. The correct publisher is Blackwell Scientific Publications of Osney Mead, Oxford.

Fyssen Foundation

1984 International Prize

The Fyssen Foundation's general aim is 'to encourage all forms of scientific enquiry into cognitive mechanisms (including thought and reasoning) underlying animal and human behaviour, into their biological and cultural bases, and into their phylogenetic and ontogenetic development'. For this purpose, a substantial International Scientific Prize shall be given for a major contribution to the progress of knowledge in the fields of research supported by the Foundation such as ethology, paleontology, archaeology, anthropology, psychology, logic and the neurosciences. It was awarded in 1980 to Prof. Andre Leroi-Gourhan, in 1981 to Prof. William H. Thorpe, in 1982 to Prof. Vernon B. Mountcastle and in 1983 to Prof. Harold C. Conklin.

Disciplines to be considered for the 1984 Prize are *Cognitive Psychology and Epistemology*. Nominations should include the curriculum vitae of the nominee, a list of his publications, and a summary (four pages maximum) of the research work upon which the nomination is based.

Nominations for the 1984 Prize should be sent (15 copies) to the Secretariat, Fyssen Foundation, 194 rue de Rivoli, 75001 Paris. The final, date for receipt of nominations is September 1, 1984.

First World Conference on Virus Diseases and Mental Health
Montreal, Canada, November 4–7, 1984.

The First World Conference on Virus Diseases and Mental Health, cosponsored by the World Health Organization and the International Comparative Virology Organization, will take place in Montreal, Canada, from November 4 to 7, 1984. This interdisciplinary conference is cochaired by Professors E. Kurstak (Montreal) and Z. J. Lipowski (Toronto) and Dr P. V. Morozov (WHO, Geneva). Prominent neurovirologists and psychiatrists will give keynote lectures.

The plenary sessions, symposia and workshops will be devoted to all the major aspects of the role of viruses in psychiatric disorders and will include: basic research on viruses in relation to the aetiology of functional psychoses and organic mental disorders; viruses and psychiatric epidemiology; diagnostic technology of viral infections of the CNS; animal models in the study of the role of viruses in mental disorders; *in vitro* studies of virus infection of neuronal cells; clinical and diagnostic aspects of psychopathology related to viral infections; perspectives on prevention and treatment of virus related mental disorders; and psychosocial aspects of sexually transmitted viral diseases (herpes, AIDS, hepatitis B).

For information and/or participation in the conference programme with a communication, please write to Professor E. Kurstak, Director, ICVO/CVRG, Faculté de Médecine, Université de Montréal, CP 6128, Succ. A, Montreal, Québec, Canada H3C 3J7. Telephone: (514) 343-6285; Telex 05 267389.

VIII International Symposium on Parkinson's Disease

Under the auspices of the World Federation of Neurology, Research Committee on Extrapyramidal Disease, the VIII International Symposium on Parkinson's Disease will be held in New York City, June 9 to 12, 1985. The Symposium is under the direction of Dr Melvin D. Yahr, President, and Dr Roger C. Duvoisin, Secretary General.

Those wishing to participate or attend should contact the Assistant Secretary General, Dr Kenneth J. Bergmann, Department of Neurology, Mount Sinai School of Medicine of the City University of New York, New York, NY 10029 USA.

Travel Grants
For Young Neuroscientists

The Guarantors of Brain are prepared to consider applications for contributions towards travel costs from neuroscientists under the age of 40 working in the United Kingdom.

1. The primary purpose of such grants is to facilitate short visits to laboratories or departments of particular relevance to the applicant's research. Applications cannot be entertained without the following documents:
   (a) An abbreviated curriculum vitae and a list of any relevant publications;
   (b) Statement of age and post currently held;
   (c) A concise account of the purpose of the proposed visit;
   (d) A recommendation from the Head of Department (where appropriate);
   (e) A letter of acceptance from the Department to be visited;
   (f) A statement of costs likely to be incurred, and of other applications for funds that have been made. Advantage should always be taken of reduced air fares when available.

2. Applications will also be considered for contributions to the cost of attending specialized symposia of particular importance to the applicant's research. Documents as in (a), (b), (c), (d) and (f) above should be submitted at least three months before the date of the meeting, accompanied by a statement of what other applications for financial aid have been made and of any contributions by the symposium organization.

3. Only exceptionally will applications for assistance to attend larger international congresses be entertained.

Successful applicants will be expected to submit a brief report on the conclusion of their visit.
Four copies of all documents should be submitted to

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London WIN 8AA

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